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Is Early Morning Urine Osmolality a Good Predictor of Response to Oral Desmopressin in Children with Primary Monosymptomatic Nocturnal Enuresis?

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Abstract The objective of this retrospective study is to evaluate the effectiveness of using early morning urine osmolality as a predictor of response to oral desmopressin in children with primary monosymptomatic nocturnal enuresis. Children treated solely with oral desmopressin for primary monosymptomatic nocturnal enuresis, between the period of January 1997 and June 2002, were recruited for the study. Early morning urine osmolality was measured before the use of desmopressin. Response to desmopressin is classified as good, intermediate or poor according to the reduction in frequency of nocturnal enuresis after eight weeks of desmopressin therapy. Total 53 patients were recruited in the study while 12 of them were excluded. Forty-one children were evaluated. Male sex is predominant. After eight weeks of treatment, thirteen children were classified as good responders, 16 as intermediate responders and 11 as poor responders. The age at treatment and the frequency of nocturnal enuresis before treatment among the three groups were comparable without any statistical significance. The early morning urine osmolality from the good responders was 791±260 mosmol/kg, from the intermediate responders was 797±168 mosmol/kg, and from the poor responders was 865±233 mosmol/kg respectively. There is no statistically significant difference in early morning urine osmolality among the three groups by the ANOVA analysis, with p value >0.05. We conclude that early morning urine osmolality is not effective in predicting the response of a child with primary monosymptomatic nocturnal enuresis to oral desmopressin therapy.

Key words Desmopressin; Early morning urine osmolality; Primary monosymptomatic nocturnal enuresis

Introduction

Nocturnal enuresis is bedwetting beyond the socially expected age of achieving bladder control during sleep, usually taken as the age of five years according to the Diagnostic and Statistical Manual of Mental Disorders-IV and International Classification of Disease-10 criteria. Primary nocturnal enuresis refers to a child who has never achieved nocturnal continence for a period of at least six months. Monosymptomatic enuresis refers to having enuresis at night only, without any associated daytime incontinence or urinary symptoms. The prevalence of nocturnal enuresis is about 15% in the paediatric age group of five, about 13% in six years old; and 10% in seven years old.[1] After the age of five, there is a spontaneous remission rate of nocturnal enuresis by 15% per year.[2] Multiple etiologies of primary nocturnal enuresis are proposed, including maturational lag and delayed development, genetics factor, nocturnal polyuria due to relative deficiency of antidiuretic hormone during night-time, infection, caffeine ingestion, and abnormal bladder function.

Poulton in 1952 has already proposed that relative nocturnal polyuria was a cause of nocturnal enuresis.[3] George et al demonstrated that there is a circadial rhythm of antidiuretic hormone secretion in human that controls the amount of urine production.[4] If there is a lack of antidiuretic hormone at night, it will lead to the production of increased amount of diluted urine. So when the amount of urine exceeds the functional bladder capacity, this would lead to bedwetting.

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The natural antidiuretic hormone in our body is vasopressin. Its secretion is controlled by the osmotic pressure and fluid volume. Norgaard et al demonstrated that about 60% of children with nocturnal enuresis tend to have nocturnal polyuria due to the relative lack of antidiuretic hormone secretion at night.[5] The urine produced is much diluted. Desmopressin is an artificial analogue of the vasopressin, which bears the effect of antidiuresis only. Desmopressin increases the water reabsorption and leads to production of reduced volume of more concentrated urine.

As the lack of antidiuretic hormone secretion is a possible causative factor in children with primary nocturnal enuresis, there are a number of studies on the effect of desmopressin treatment in enuretic children. The Cochrane Database System Reviews has reviewed the effectiveness of desmopressin for the treatment of children with primary nocturnal enuresis.[6] When compared with placebo group, those treated with desmopressin had at least one fewer wet night, and increased the chance of achieving 14 consecutive dry nights. Besides desmopressin is a safe drug with little adverse effects reported in the literatures.

Early morning urine osmolality is a reflection of the concentration of urine that is produced at night. Therefore those children with relative lack of nocturnal antidiuretic hormone release would be expected to have a lower early morning urine osmolality. In our study, we would like to evaluate whether we could use the early morning urine osmolality in predicting the group of enuretic children, in whom desmopressin treatment would be more beneficial.

Patients and Method

This is a retrospective study. Between the period of January 1997 to June 2002, the medical records of the children with the diagnosis of primary monosymptomatic nocturnal enuresis were retrieved. Those who were older than seven years old were selected. After the detailed history taking and physical examination, only those with primary monosymptomatic nocturnal enuresis equal or greater than three nights per week were included. Initial investigations including urinalysis, urine culture, early morning urine osmolality and renal function test were performed. Behavioural modifications including restriction of fluid intake before bedtime, avoidance of diuretics like caffeine, and voiding before going to bed were advised. Star Chart as a record of frequency of nocturnal enuresis and as a positive reinforcement behavioral therapy was started first.

However if the frequency of nocturnal enuresis in the child still persisted equal or greater than three times per week after the trial of behavioural modification, the family will be further discussed on the choice of other modalities of treatment including oral desmopressin or enuretic alarmas. Only those who agreed for oral desmopressin treatment will be given 0.2 mg desmopressin before bedtime. Those who completed the eight weeks course of oral desmopressin afterwards were included in this study. The children with abnormal urinalysis, positive urine culture suggestive of urinary tract infection, underlying organic cause of enuresis, or those with prior treatment with oral desmopressin or other medications for nocturnal enuresis, those with prior treatment with enuresis alarm were all excluded from the study.

Star Chart is used as a diary to record down the frequency of nocturnal enuresis during these eight weeks course of desmopressin therapy. The average nights per week with enuresis before starting oral desmopressin therapy were calculated from the preceding two consecutive weeks. The patients were evaluated at the eighth week after starting treatment, and the average nights per week with enuresis after completion of treatment was calculated by averaging the number of bedwetting night in the last two weeks, i.e. the seventh and eighth week.

The responses of the patients to oral desmopressin therapy at the end of the eighth week were classified into three groups according to the average number of nights with enuresis per week. A good responder is defined as those with reduction of ≥90% in the average number of bedwetting nights per week; the intermediate responder is the one with reduction of ≥50% but <90% in average number of bedwetting nights per week; and the poor responder is the one with reduction of <50% in average number of bedwetting nights per week respectively. The children with incomplete eight weeks of treatment are excluded from the study.

The age of the children at starting treatment, the average number of nights with enuresis per week, and the early morning urine osmolality before starting desmopressin treatment from these three groups of patients were collected. The urine osmolality was measured with the Advanced micro-osmometer Model 3300 from Advanced Instrument, Inc. Norwood, Massachusatts, USA. The one-way ANOVA statistical method is used to compare any statistical significant differences among the three groups. It is statistical significant if the $p \leq 0.05$.

Results

Between the period January 1997 to June 2002, there were a total of 249 children with the diagnosis of primary monosymptomatic nocturnal enuresis from the records. Out of these 249 children, 124 of them were older than seven years old with bedwetting frequency of equal to or more than three nights per week. Fifty-three of these 124 children were treated with oral desmopressin and included in this study. After the completion of the eight weeks treatment, only 41 of the 53 children were recruited in the study. Twelve of them were excluded as nine had incomplete follow up for evaluation, two were mentally retarded, and one had microscopic haematuria.

Among the 41 children, 32 of them were male and nine were female. Their ages at starting treatment ranged from 74 to 163 months. At the end of the eighth week, 13 children were classified as good responders, 17 were intermediate responders, while 11 were poor responders. Table 1 showed the results of sex ratio, age (months), pre-treatment bedwetting frequencies (nights per week), and early morning urine osmolality (mosmol/kg) among the three groups.

The one-way ANOVA test did not show any statistically significant differences in the age of presentation, the pre-treatment bedwetting freqeuency and early morning urine osmolality among the good, intermediate or poor responders.

Discussion

Primary nocturnal enuresis is a common problem in paediatric age group with male predominance. Desmopressin is a choice of treatment for these children. In our group of children, their response to oral desmopressin treatment was evaluated after 8 weeks of treatment. The response at eighth week was selected as it was shown that the response to oral desmopressin was prominent after 4 weeks of treatment, which lasted till completion of 12 weeks of therapy (unpublished data from the Hong Kong Childhood Enuresis Study Group).

The responses of enuretic children to oral desmopressin was classified into three different groups according to the reduction in average number of bedwetting nights per week. The sex ratio among the three groups was similar, and though the male gender was predominant, it did not affect their responses to oral desmopressin treatment. We found that the ages of these three groups of children were comparable to each other at the time of starting treatment. Therefore the different responses were not related to the ages of children though a longitudinal study showed that 15% of the enuretic children would spontaneously recover every year.[2]

Nocturnal polyuria due to the lack of antidiuretic hormone during nighttime was proposed as a causative factor for primary nocturnal enuresis,[3] resulting in the production of increased amount of diluted urine. However, Kawauchi et al did not find any statistically significant differences in the early morning urine osmolality between 144 enuretic and 1453 non-enuretic children.[7]

Besides, Kruse et al has studied the predictive factors in treatment of primary monosymptomatic nocturnal enuresis with desmopressin.[8] They studied 399 children with ages of 6 to 12, the study concluded that those having fewer wet nights had a better response to treatment. However in our patients, the frequency of wet nights before treatment were comparable among the three groups. Therefore the different responses among them were not accounted for by the frequency of wet nights before starting oral desmopressin treatment.

Regarding the effectiveness of using early morning urine

Table 1 Comparison among the good, intermediate and poor responders

	Good responders	Intermediate responders	Poor responders	P-value by one way ANOVA
No	13	17	11	
Male:Female	11:2	12:5	9:2	
*Age (months)	116±27	107±18	103±13	0.32
*Pre-treatment bedwetting frequencies (nights/week)	5.7±1.9	5.6±1.5	5.6±1.5	0.96
*EMU osmolality (mosmol/kg)	791±260	797±168	865±233	0.66

*The age, pre-treatment bedwetting frequencies and EMU osmolality are expressed as mean±2SD

osmolality as the predictive factor to oral desmopressin treatment, the early morning urine osmolality is the reflection of concentration power of the kidneys at night, which can be used to select the group of children with relative nocturnal polyuria. In our own study, the early morning urine osmolality was measured in the children before starting treatment, and all the children were treated with the same dose of desmopressin in spite of their early morning urine osmolality values. We found that the urine osmolality values were not statistically different among the three groups of children, and so we suggest that early morning urine osmolality is not a good predictor in selecting the group of children with better responses to oral desmopressin therapy.

From the literature, there are various studies concluding that urine osmolality is not a good predictor of response to desmopressin in the treatment of monosymptomatic nocturnal enuresis. Rushton et al studied 96 children aged 8 to 14 years old, and concluded that children treated with desmopressin showed a significantly higher 6 am urine osmolality and a higher 6 am to 6 pm urine osmolality ratio. However within the desmopressin treatment group, the difference between the responders and the nonresponders was not statistically significant.[9]

Folwell et al showed no statistical significance in the changes of urine osmolality between the responders and non-responders to desmopressin treatment.[10] Among the 37 children they studied, they found that those non-responders tended to achieve a maximum overnight urine osmolality >1000 mosmol/kg during desmopressin treatment as compared with the responders. Eller et al concluded spot urine osmolality was not predictive of the response to desmopressin in treatment of nocturnal enuresis.[11]

Though early morning urine osmolality is not shown to be a good predictor for those with primary nocturnal enuresis under desmopressin treatment, other factors were shown to be more predictive of poor treatment responses. These included: younger age, more wet nights per week, multiple wetting episodes per night and the first wetting episode occurring before midnight.[8] Probably it needs further prospective studies to show whether there are other or better predictive factors in selecting those with response to desmopressin treatment.

Our study had several limitations. Firstly, this is a retrospective study and there may be bias in selecting treatment for the children. Oral desmopressin was offered to those children after discussion and agreement with parents. The factor of parental attitude could not be considered separately in the choice of treatment. Secondly, the duration of using Star Chart before starting oral desmopressin was not constant among the children. Star Chart itself is one kind of behavioral therapy for primary nocturnal enuresis. However from our data, the frequencies of bedwetting nights per week were comparable among the three groups of children before starting desmopressin treatment. Thirdly, the difference in responses may be related to the dose of oral desmopressin therapy, as some children may require a higher dose than 0.2 mg for a significant reduction of nocturnal enuresis. Therefore it is better to carry out a prospective randomised control study to evaluate the effectiveness of using early morning urine osmolality in predicting the response to oral desmopressin therapy. We can stratify the early morning urine osmolality into different categories and treat with either placebo or desmopressin, and then study whether there is any statistical difference in those responders and non-responders.

In conclusion, measuring the early morning urine osmolality is not very effective in selecting the group of children with primary monosymptomatic nocturnal enuresis who will show a better response to an eight-week course of oral desmopressin 0.2 mg given before bedtime.

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