New treatment protocol for primary nocturnal enuresis in children according to ultrasound bladder measurements

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ABSTRACT

الأهداف: تقييم النماذج المختلفة لعلاج سلس البول الليلي الأولي لدى الأطفال وفقاً لنتائج تصوير المثانة بالموجات فوق الصوتية (حجم المثانة، ومدخلات سماكة جدار المثانة) (BVWI).

الطريقة: أُجريت هذه الدراسة في كلية الطب – جامعة أصفهان – أصفهان – إيران، خلال الفترة مابين فبراير 2006م وحتى نوفمبر 2007م، وشملت 31 طفلاً، تراوحت أعمارهم ما بين 6-12 عاماً. بناءً على (حجم المثانة وسماكة جدارها) (BVWI)، تم تقسيمهم إلى ثلاث مجموعات كالتالي: المجموعة الأولى (BVWI <70%) وتم علاجها بعقار ديسموبريسين عبر الفم وعقار أوكسيبوتينين. المجموعة الثانية (BVWI 70% - <130%) تم علاجها بعقار ديسموبريسين عبر الفم. المجموعة الثالثة (BVWI >130%) تمت معالجتها بعقار ديسموبريسين عبر الفم متحداً مع تقنية الطرح المزدوج والطرح المجدول. تمت معالجة المجموعات الثلاثة لمدة لثلاثة أشهر.

النتائج: كان هناك انخفاض ملحوظ في تكرار التبول في الفراش قبل وبعد دورة المعالجة الأولى لجميع المجموعات ($p<0.05$). بلغ معدل الاستجابة الكاملة 70%، 25%، 20% في المجموعة الأولى، المجموعة الثانية والمجموعة الثالثة على التوالي. كما بلغ معدل الاستجابة الكاملة والجزئية 9 من 10 من الأطفال في المجموعة الأولى (90%)، 13 من 16 طفل في المجموعة الثانية(81%)، 3 من 5 أطفال في المجموعة الثالثة (60%). انخفض تكرار التبول في الفراش بشكل ملحوظ عند دورة العلاج الأولى والثانية في المجموعة الثانية ($p<0.05$).

خاتمة: حقق تمثيل المعالجة المقترحة وفقاً لقياسات تصوير المثانة بالموجات فوق الصوتية معدل استجابة مفضلة لدى الأطفال الذين يعانون من سلس البول الليلي الأولي. نقترح هنا، وجوب استعمال هذه الطريقة لتطوير معالجة سلس البول لدى الأطفال.

Objective: To evaluate the response rate of various modalities of therapy in primary nocturnal enuretic children according to the ultrasound bladder volume and wall thickness index (BVWI) measurements.

Methods: From February 2006 to November 2007, a total of 31 children, aged 6-12 years old were enrolled in a clinical trial at the Faculty of Medicine, Isfahan Medical University, Isfahan, Iran. Based on BVWI they were divided into 3 groups as follows: Group 1 (BVWI <70%) was treated with oral desmopressin and oxybutynin; Group 2 (BVWI70%to<130%) was treated with oral desmopressin. Group 3 (BVWI>130%) was treated with oral desmopressin accompanied by double-voiding technique and scheduled voiding. All of them were treated for 3 months.

Results: Significant reductions in mean bed-wetting frequency before and after first treatment cycle were observed in all groups ($p<0.05$). The complete response rate was 70% in Group 1, 25% in Group 2, and 20% in Group 3. Overall, the complete and partial response rate was 9/10 (90%) children in Group 1, 13/16 (81%) in Group 2, and 3/5 (60%) in Group 3. Bedwetting frequency significantly decreased at the first and second treatment cycles in Group 2 ($p<0.05$) for each pair wise comparison.

Conclusion: The proposed treatment representation according to ultrasound BVWI measurements achieves favorable response rates in children with PNE. We suggest that this treatment should be used to develop the management of enuresis in children.

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Primary nocturnal enuresis (PNE) is one of the most frequent urological complaints in pediatrics.[1] Nocturnal enuresis produces many emotional, social and psychological disturbances for patients and their families. The reported prevalence in Iran is 8.8% to 3.7% among 6-12-year-old children.[2] The most common pathophysiological factors contributing to nocturnal enuresis include decreased functional bladder capacity, impaired arousal from sleep and nocturnal polyuria due to a relative deficiency of anti-diuretic hormone.[3] Ultrasound (US) measurement of bladder wall thickness can be used as a predictor of bladder dysfunctions in children.[4,5] Yeung et al[6] showed that enuretic children with good response to treatment had normal bladder capacity as determined by bladder volume and wall thickness index (BVWI%), whereas poor response to treatment was significantly associated with pathological bladder conditions. In our previous study, normal bladder function was seen in 67% children with PNE.[7] According to the pathophysiology of PNE, desmopressin is used to provocation of the antidiuretic effect at the kidney level.[8] It has a rapid onset of effect and can be administrated intranasal or orally. Seasonal allergies and upper respiratory infections may impair intra-nasal absorption. Convenience and ease of use are advantages of the oral over the intra-nasal form.[3] Decreased functional bladder capacity due to detrusor hyperactivity is regarded as a major pathogenic factor in nocturnal enuresis.[9] Oxybutynin, an anticholinergic drug with direct smooth muscle relaxing properties, should be considered in this situation alone or as a combination therapy.[9] In Persson-Junemann's et al[10] study 70% of the patients with PNE who responded to oxybutynin had small bladders.[10] Neveus et al[11] showed that 61% non-responders children to standard enuresis treatment responded to combination oxybutynin and desmopressin. According to ultrasound BVWI measurements, we evaluated the response rate of PNE children to 3 different regimen; oxybytinine and oral desmopressin, oral desmopressin, oral desmopressin accompanied by double-voiding technique and schedule voiding.

Methods. The study was performed between February 2006 to November 2007 at the Faculty of Medicine, Isfahan Medical University, Isfahan, Iran. A total of 52 children aged 6-12 years old, with a documented history of primary nocturnal enuresis were enrolled in a clinical trial. Before commencing the study, approval was granted by the University Ethics Committee. Informed consent was obtained from all families. Urological, cardiovascular and neurological diseases, daytime urinary incontinence, upper airway obstruction, diabetes, urinary tract infection and hypercalciuria were regarded as exclusion criteria. No patient used any drug or conditioning therapy for NE during the 30 days before study entry. Physical examinations were conducted at the first visit. In the second morning, urine sample calcium and creatinine were assessed. Urine cultures were performed in all patients. Ultrasonographic examination of the urinary system was performed on all patients. Scans were performed with the patient supine using Toshiba Just vision 200 with a 5 MHz frequency probe. Children were scanned in a standard supine position. Both renal volumes were measured. The bladder volume index was calculated based on the equation, BVI = longitudinal plane (LS) times maximum transverse plane (TS) times maximum anteroposterior diameter (AP). The BVI was repeated and bladder emptying efficiency was calculated from BVI maximum - BVI empty/BVI maximum as a percentage. The mean bladder wall thickness was calculated as an average of the 3 measurements (BT = [anterior wall thickness plus lateral wall thickness plus posterior wall thickness]/3). The bladder volume and wall thickness index were calculated as bladder volume and wall thickness index (BVWI%) = (measured BVI maximum/measured BT). This volume was expressed as a percentage of the expected from reference standard values of children with a normal urinary tract in accordance with the study of Leung et al.[12] According to BVWI measurements enuretic children was divided into 3 groups as follows: Group 1: BVWI <70% (implying smaller bladders with a thicker wall), Group 2 BVWI: 70% to <130% (implying normal bladders), Group 3 BVWI: >130% (relatively larger bladder capacity with relatively thinner walls). Patients in Group 1 were treated with 0.1 mg desmopressin tablet (Minirin) and 5 mg oxybutynin one hour before bedtime every night. Patients in Group 2 were treated with 0.1 mg desmopressin tablet one hour before bedtime every night. Patients in Group 3 were treated with 0.1 mg desmopressin tablet one hour before bedtime every night accompanied by double-voiding technique and schedule voiding. All of them were treated for 3 months. The children were evaluated as outpatients every 4 weeks. During the inclusion period 21 of 53 children withdrew the study. Reasons for discontinuation included loss to follow-up, noncompliance with the dosing regimen and absence of post baseline record data. There were no withdrawals for adverse events. The families were given a diary in which they recorded dry and wet nights for 2 weeks before medication and as long as study intervals. During the treatment months patients were instructed to empty the bladder and not drink too much fluid before bedtime. Fluid intake and urine production were not recorded and no blood samples were taken. According to the number of wet nights after 4 weeks of treatment,

the patients were defined as complete responders (dry or more than 90% reduction in wet nights compared to baseline), partial responders (50-90% reduction) and non-responders (less than 50% reduction). The families were asked to record any possible side effects of the medication.

Statistical analysis. The data were compiled and analyzed using the Statistical Package for Social Sciences (SPSS 11.5) program. Comparisons were made using repeated measure test within group design. Remission rate was analyzed for each treatment groups by Kaplan-Meier curve. Results were considered statistically significant when $p<0.05$.

Results. The study groups composed of 31 students' aged 6-12 years (5 were aged 6-7 years, 6 were 7-8, 8 were 8-9, 6 were 9-10, 3 were 10-11 and 3 were 11-12 years) with primary nocturnal enuresis. There were 16 males (51.6%) and 15 females (48.4%). Only 20.7% of children had no family history of enuresis. Twenty-four (77.43%) of them had more than 3 wet nights per week. The patients were subdivided based on BVWI measurements into 3 groups: Group 1 consisted of 10 children (32.3%) with BVWI <70%, Group 2 consisted of 16 children (51.6%) with 70% <BVWI <130%, Group 3 consisted of 5 children (16.1 %) with BVWI >130%. They remained on the assigned treatment groups for the entire 3 months duration of study. Significant reductions in bed-wetting were observed at all groups. Pair wise comparisons of bedwetting frequency in each group were shown in **Table 1**. Of the 10 patients in first group, 7 versus 3 responded completely to the 0.1 mg daily dose of oral desmopressin and 5 mg oxybutynin continued treatment for 3 months. Of the 16 patients in second group, 4 versus 12 responded completely to the 0.1 mg daily dose of oral desmopressin. Of the 5 patients in latter group, one versus 4 responded completely to the 0.1 mg daily dose of oral desmopressin accompanied by double-voiding technique and schedule voiding. The complete and partial response rate was 90% in group 1, 81% in group 2 and 60% in group 3. The detailed

Table 1 - Comparisons of mean bed-wetting frequency before and after treatment during 3 months follow-up.

Mean wet nights/month	Mean difference	95% confidence interval of differences		*P* value
		Lower	Upper	
Group 1 - BVWI <70%				
Before treatment (22.1±8.96)				
First month (8.6±7.0)	13.500	8.039	18.961	0.000
Second month (6.1±6.19)	16.000	10.819	21.181	0.000
Third month (5 ±8.39)	17.100	10.497	23.703	0.0001
First month of treatment (8.6±7.0)				
Second month (6.1±6.19)	2.500	0.282	4.718	0.031
Third month (5 ±8.39)	3.600	-0.883	8.089	0.103
Second month of treatment (6.1±6.19)				
Third month (5 ±8.39)	1.100	-2.263	4.463	0.478
Group 2 - BVWI 70% - <130%				
Before treatment (20.4 ± 7.09)				
First month (9.53±4.98)	11.563	8.215	14.910	0.000
Second month (6.66±3.39)	14.500	10.618	18.382	0.000
Third month (6.60±4.48)	14.625	10.715	18.535	0.000
First month of treatment (9.53±4.98)				
Second month (6.66±4.48)	2.938	0.382	5.493	0.027
Third month (6.60±4.48)	3.063	0.167	5.985	0.040
Second month of treatment (6.66±3.39)				
Third month (6.60±4.48)	0.125	-1.235	1.485	0.847
Group 3 - BVWI >130%				
Before treatment (16 ± 9.35)				
First month (9.4±7.33)	6.600	2.335	10.865	0.013
Second month (7±4)	9.000	-.166	18.166	0.053
Third month (6.60±4.48)	9.000	-.537	18.537	0.059
First month of treatment (9.4±7.33)				
Second month (7±4)	2.400	-5.334	10.134	0.438
Third month (6.60±4.48)	2.400	-5.482	10.282	0.446
Second month of treatment (7±4)				
Third month (7±4.89)	0.000	-2.483	2.483	1.000

BVWI - bladder volume and wall thickness index

Table 2 - The treatment response rates in children with primary nocturnal enuresis (PNE) according to bladder volume and wall thickness index (BVWI%) measurements during 3 months of follow-up.

Treatment period/response rate	Group 1 n=10 BVWI <70%	Grope 2 n=16 BVWI 70% to <130%	Group 3 n=5 BVWI >130%
First treatment period			
Complete	3 (30)	0	1 (20)
Partial	3 (30)	11 (69)	1 (20)
Non-responder	4 (40)	5 (31)	3 (60)
Second treatment period			
Complete	6 (60)	2 (12)	0
Partial	3 (30)	10 (63)	3 (60)
Non-responder	1 (10)	4 (25)	2 (40)
Third treatment period			
Complete	7 (70)	4 (25)	1 (20)
Partial	2 (20)	9 (56)	2 (40)
Non-responder	1 (10)	3 (19)	2 (20)

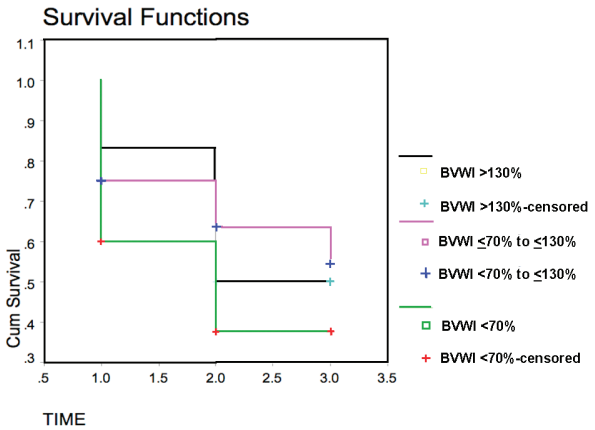

Figure 1 - The remission probability of children with primary nocturnal enuresis following treatment in 3 different groups according to bladder volume and wall thickness index (BVWI%) measurement.

results are shown on **Table 2**. The remission probability of children with primary nocturnal enuresis following treatment in 3 different groups according to BVWI measurement was shown in **Figure 1**.

Discussion. Primary nocturnal enuresis is one of the most common developmental disorders among children and often leads to considerable distress in affected children and their parents. Although there are many treatment modalities, pharmacotherapy is the most popular. The proposed treatment representation according to ultrasound measurements of bladder wall thickness achieves favorable response rates in the treatment of children with PNE. Yeung et al[6] reported that ultrasound measured bladder volume and wall thickness index could be used as a sensitive tool for the clinical assessment of children with primary nocturnal enuresis. Bladder volume and wall thickness index correlated well with the presence or absence of underlying bladder dysfunction.[4,5] In our study, ultrasound (US) measurement of BVWI was used to predict functional bladder capacity and the response rate to different types of therapy. Desmopressin reduces bedwetting by decreasing the amount of urine produced at night. It was shown that desmopressin was more effective than placebo in reducing bed-wetting in children with PNE but this effect was not sustained at short period of time.[13] Wolfish et al[14] showed that the response rate (>50% reduction in bet-wetting over baseline) to desmopressin remained constant at approximately 74% for 12 months period in 112 enuretic children and they recommended continuing treatment for longer periods. There were insufficient data to reliably show that a higher dose of desmopressin was more effective than a lower dose.[4] In this study in order to minimize side effects and costs, the lowest dose was used, but the treatment course was only 3 months. More than 50% reduction in bet-wetting over baseline was seen in 81% in our patients with normal bladder. The lower response rate in children with larger bladder capacity with relatively thinner walls should be probably due to inadequate cooperation of parents and children to follow the double-voiding technique and schedule voiding. Efficacy of oxybutynin in nocturnal enuresis was examined in a few studies. In most of them children also had the daytime symptoms.[10,15,16] Nearly all of them were uncontrolled trial, the response rate was between 47-70% and responder had low bladder capacity.[10,17-19] In a muticenteric study in Italy, of the 48 children with diurnal voiding disturbances and enuresis, the success rate was 54% in those treated with oxybutynin alone and 71% in those treated with both oxybutynin and desmopressin[11] Martin-Crespo and Luque[18] showed that combination therapy with oxybutynin and desmopressin could be a good choice of treatment in children with bladder hyperactivity that was

confirmed by urodynamic study. Lee et al[19] also revealed that combination therapy with desmopressin plus oxybutynin comparison to desmopressin or imipramine gave significantly faster and more cost-effective results. In this study, none of our children had the daytime symptoms and combination therapy was used in children with small bladder as confirmed by a non-invasive modality and the complete response rate was significant. In Nevous et al[11] study, renal concentrating capacity and functional bladder capacity were compared between 67 children with PNE who were treated with desmopressin, oxybutynin, combination therapy and 55 dry children as controls.[9] They demonstrated that enuretic children responding to oxybutynin have small bladders and probably hyperactive detrusors, whereas those responding to desmopressin or who need both drugs have polyuria. In their study, the average bladder capacity at each void, was defined as average daytime functional bladder capacity.[9] By contrast, in this study the functional bladder capacity was measured by ultrasound. Using a sensitive method as ultrasound measured bladder capacity should probably increased the response rate (>50% reduction in bet-wetting over baseline) in children with PNE who received this proposed therapy. However, it must be noted that the population studied was not large, the treatment course was short and a double blind trial is needed to avoid bias and consider placebo effect.

In conclusion, ultrasound measured bladder parameters was used to differentiate the primary nocturnal enuresic children into different treatment subtypes. The overall complete and partial response rate was 90% in patients with a low bladder capacity, 81% with a normal bladder and 60% with a larger bladder capacity. A larger double-blind clinical trial is required to define who will benefit from this treatment strategy.

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