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Effect of desmopressin lyophilisate (MELT) plus anticholinergics combination on functional bladder capacity and therapeutic outcome as the first-line treatment for primary monosymptomatic nocturnal enuresis: A randomized clinical trial

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Purpose: To assess the efficacy of desmopressin plus anticholinergic combination therapy as first-line treatment for children with primary monosymptomatic nocturnal enuresis (PMNE) and to analyze this combination's effect on functional bladder capacity (FBC).

Materials and Methods: A total of 99 children with PMNE were prospectively enrolled from 2015 to 2019 and randomly allocated to a monotherapy group (n=49), with oral desmopressin lyophilisate (MELT) only; and a combination group (n=50), with desmopressin plus an anticholinergic (propiverine 5 mg). Efficacy and FBC were evaluated at 1 and 3 months after treatment initiation; the relapse rate was assessed at 6 months after treatment cessation.

Results: The combination therapy group showed a higher rate of complete response than the monotherapy group after 3 months of treatment (44.0% vs. 22.4%, p=0.002). A significant increase in mean FBC was observed only in the combination group, from 88.72±26.34 mL at baseline to 115.52±42.23 mL at 3 months of treatment (p=0.024). Combination therapy was significantly associated with treatment success at 3 months after treatment initiation (odds ratio [OR], 3.527; 95% confidence interval [CI], 1.203–6.983; p=0.011) and decreased risk of relapse at 6 months after treatment cessation (OR, 0.306; 95% CI, 0.213–0.894; p=0.021), by multivariable analysis.

Conclusions: This study represents the first prospective, randomized controlled trial showing higher response rates and lower relapse rates with desmopressin plus anticholinergic combination therapy compared with desmopressin monotherapy as first-line treatment for children with PMNE.

Keywords: Cholinergic antagonist; Deamino arginine vasopressin; Nocturnal enuresis; Prospective studies

INTRODUCTION

Approximately 15% of 5-year old children have nocturnal enuresis (NE), and about 80% of these cases are primary NE, which is distinguished from secondary NE, defined as bedwetting that develops after a child has remained dry at

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night for at least 6 months [1]. Most children with primary NE have no lower urinary tract symptoms (LUTS), such as daytime urinary frequency, urgency, or urinary incontinence; this is referred to as primary monosymptomatic NE (PMNE) by the International Children's Continence Society (ICCS) [2].

Desmopressin is the most widely used first-line treatment for PMNE, although it is associated with unsatisfactory outcomes and high relapse rates (60%–80%) [3]. Anticholinergic agents are currently not recommended as the first-line treatment for PMNE. However, in 57% to 66% of children who undergo unsuccessful initial treatment, a combination of an anticholinergic drug with desmopressin has been reported to be effective [3-5]. It is most beneficial in patients with LUTS, including those with non-monosymptomatic NE [6]. In the absence of daytime bladder overactivity or LUTS, anticholinergic agents are thought to have little effect in managing PMNE [4]. Nevertheless, previous studies have shown that children with a larger bladder capacity are more likely to exhibit successful responses, and functional bladder capacity (FBC) is a reliable predictor of a good response to desmopressin [4,7]. These results suggest a combination of desmopressin and anticholinergics may be useful, since they act to prevent NE via different mechanisms: desmopressin reduces urine production at night, while anticholinergic agents enable the bladder to store more urine. Based on this, we hypothesized that desmopressin with anticholinergic as first-line treatment for PMNE would have higher response rate than desmopressin alone.

Therefore, the purpose of this study was to analyze the impact of FBC on treatment success and relapse following treatment, and to determine whether a combination of desmopressin lyophilisate (MELT) plus anticholinergic agents was superior to desmopressin monotherapy, not only for desmopressin non-responders and patients with non-monosymptomatic NE but also as a first-line treatment for PMNE.

MATERIALS AND METHODS

1. Overview and patient enrolment

In this single institution study, patients were selected from those referred to Hallym University Sacred Heart Hospital Pediatric Urology Clinic for the treatment of NE between January 2015 and August 2019; 136 children prospectively recruited. Of these, the parents of 12 children refused to participate or withdrew their consent; 10 children were excluded by screening, which was performed before enrolment and treatment initiation; and 9 patients

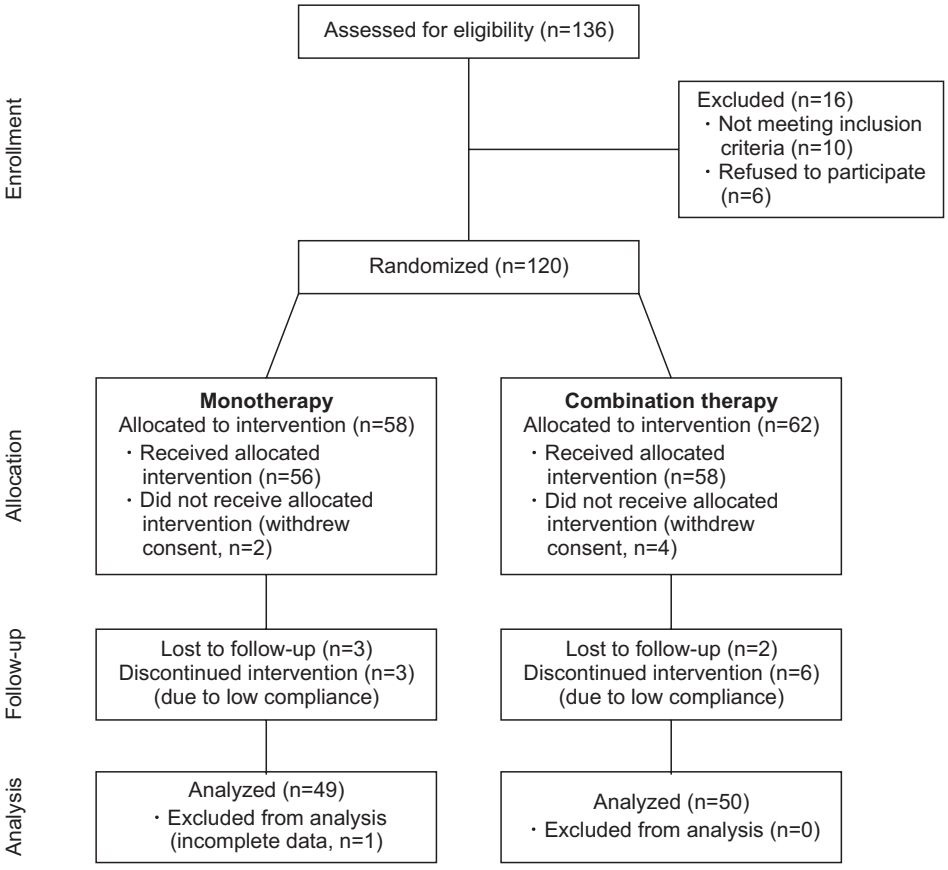

Fig. 1. Study design with flow chart.

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dropped out because of compliance issues around completing 24-hour frequency volume charts (FVC) and/or adequate medication. Excluding 6 more patients due to follow-up loss or incomplete data, 99 children were included in the final analysis (Fig. 1). The study protocol was approved by the Institutional Review Board Committee at Hallym University Sacred Heart Hospital (approval number: 2016-I001); written informed consent was obtained from each participant's caregiver before enrolment. The trial was registered in the Clinical Research Information Service (CRIS) of Korea (CRIS registration number: KCT0005178).

2. Inclusion/exclusion criteria

Patients aged between 6 and 14 years who had PMNE and had not been treated for enuresis for at least 6 consecutive months before enrolment were eligible. Among them, a total of 52 children (29 vs. 23 children in monotherapy and combination therapy group, respectively) had sought treatment for enuresis 6 months before enrolment. Patients were excluded if they had daytime incontinence, increased or decreased voiding frequency (>8 or ≤3 times/day), urgency or bowel elimination problems (e.g., encopresis or constipation). Constipation was defined according to the Rome II criteria and the Paris Consensus on Childhood Constipation Terminology Group [8]. Children with known allergies to anticholinergic therapy, a history of gastrointestinal disorders, or uncontrolled, narrow-angle glaucoma were also excluded.

3. Study design and outcome measurement

All children underwent a baseline evaluation, which included history-taking and a general physical examination by a pediatric urologist. Demographic data, caregiver information, and symptom severity were recorded. Obesity was noted (defined as having a body mass index ≥95th percentile for age and sex) [9]. Screening included 3 days of 24-hour FVC and elimination records to identify LUTS and bowel elimination problems. On their second visit, eligibility screening was done by a research coordinator, followed by generation of a unique number by a computer system to allocate the patients. The randomization sequence was concealed until treatment groups were assigned. As a result, patients were randomly allocated into one of two treatment groups: monotherapy group, desmopressin lyophilisate (MELT) 120 μg only; combination therapy group, desmopressin lyophilisate (MELT) 120 μg plus propiverine 5 mg. Propiverine was prescribed as 0.5 tablet of powered from of BUP-4 Tab (Jeil Pharm CO., LTD., Seoul, Korea) 10 mg. Treatment was then initiated and children and caregivers were instructed to take the medication just before bed. Patients were also instructed to refrain from water intake 3 hours before bedtime. The primary and secondary endpoint was the effectiveness of treatment and relapse of enuresis after treatment, respectively. The effectiveness of treatments were evaluated at the third and fourth visits (1 and 3 months post-treatment, respectively), using the ICCS criteria, as follows: complete response (CR), defined as full resolution of NE; partial response (PR), defined as a 50%–99% decrease in NE incidence; and nonresponse (NR), defined as a decrease in NE incidence ≤49% [10]. Completed 3-day, 24-hour FVC were obtained from all patients at these visits to analyze changes in FBC. Although there is criticism that maximal voided volume during day-time does not accurately reflect bladder capacity in patients with enuresis [11], the traditional definition of FBC which is the largest voided volume except first morning void observed in FVC was used in this study to simplify the analysis. Following the 3-month treatment period, patients showing CR were discontinued with treatment. They were then recalled for a follow-up visit, 6 months after cessation of treatment, to evaluate NE relapse, defined as PR+NR. In addition, adverse events related to desmopressin or propiverine were collected at each visit and severity was recorded as grade 0–4 according to the common terminology criteria for adverse events version 4.0 (CT-CAE ver. 4.0).

4. Statistical methods

The sample size was determined by reference to previous studies, which showed a higher treatment success rate of 25%–28%, following combination therapy compared with monotherapy [1,12]. Therefore, the number of patients was calculated with the expectation that the combination therapy group's success rate would be about 25% higher than that of the control group. Accordingly, the sample size was set at 50 patients in each treatment arm, with a 2-sided significance level of 0.05 with 80% power, considering a 10% dropout rate. Statistical comparisons between the groups were made using the Kruskal–Wallis test or a Student's t-test for continuous variables and the chi-squared test for categorical variables. Logistic regression models were used to investigate the effect of treatment method (monotherapy versus combination therapy) on treatment success and relapse, with adjustment for potential confounding factors. All statistical analyses were performed using SPSS® for Windows ver. 24.0 (Statistical Package for Social Sciences™; IBM Corp., Armonk, NY, USA); a p-value of <0.05 was considered statistically significant.

Table 1. Patient characteristics

Variable	Overall (n=99)	Desmopressin monotherapy (n=49)	Combination therapy (n=50)	p-value
Age (y)	7.51±1.83	7.68±1.98	7.35±1.84	0.158
Sex				0.895
Boys	65 (65.7)	33 (67.3)	32 (64.0)	
Girls	34 (34.3)	16 (32.7)	18 (36.0)	
Caregiver				0.450
Mother	66 (66.7)	34 (69.4)	32 (64.0)	
Grand mother	30 (30.3)	13 (26.5)	17 (34.0)	
Others	3 (3.0)	2 (4.1)	1 (2.0)	
Caregiver's age (y)	47.50±5.98	46.18±5.32	48.80±6.14	0.659
Caregiver's educational status				0.578
Secondary or lower	5 (5.1)	3 (6.1)	2 (4.0)	
High school	48 (48.5)	25 (51.0)	23 (46.0)	
University degree	46 (46.4)	21 (42.9)	25 (50.0)	
Obesity	7 (7.1)	3 (6.1)	4 (8.0)	0.953
Positive family history	48 (48.5)	26 (53.1)	22 (44.0)	0.374
Baseline enuresis episodes per month	25.29±4.51	25.42±4.82	25.18±3.52	0.683
Functional bladder capacity (mL)	89.35±24.57	90.52±23.85	88.72±26.34	0.684
Nocturnal urine volume (mL)	211±75	235±52	189±81	0.079

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

RESULTS

The study population included 65 boys and 34 girls, with a mean age of 7.51±1.83 years. Most caregivers were the mothers of the children (66.7%), and the majority of caregivers had an education level higher than high-school graduate (94.9%). There were no notable differences in patient demographics, including age, sex, caregiver characteristics, symptom severity, or FBC between monotherapy and combination therapy group (Table 1).

At baseline, the mean number of enuresis nights per month for patients in the monotherapy and combination therapy groups were 25.42±2.82 and 25.18±3.52, respectively (p=0.683). After 1 month of treatment, the mean number of enuresis nights showed a significant difference between the monotherapy and combination therapy groups (10.99±3.12 and 8.02±3.27, respectively, p=0.002) (Fig. 2A), and this significant difference persisted after 3 months of treatment (5.98±3.13 and 2.60±2.38, respectively, p<0.001) (Fig. 2A). The mean FBC value showed no significant difference between the monotherapy and combination therapy groups at baseline (90.52±23.85 mL and 88.72±26.34 mL, respectively, p=0.684). In the monotherapy group, the mean FBC value changed from the baseline to 93.24±29.17 mL and 92.73±21.38 mL following 1 and 3 months of treatment, respectively (all, p>0.050, Fig. 2B), whereas in the combination therapy group, the mean FBC value changed significantly from the baseline to 107.29±37.11 mL (p=0.031) and 115.52±42.23 mL (p=0.024) after 1 and 3 months of treatment, respectively (Fig. 2B). When patients were stratified by treatment response, mean FBC of patients with NR or PR and CR did not show a significant difference at baseline (85.28±34.92 mL and 82.43±25.48 mL, respectively, p=0.536), whereas they showed a significant difference at 3 months after treatment (111.59±42.5 mL and 126.33±40.8 mL, respectively, p=0.045) (Fig. 2C).

After 3 months of treatment, 11 (22.4%) of patients showed CR in the monotherapy group, which was significantly lower than the 22 (44.0%) patients in the combination group (p=0.002). A. NR was observed in just 3 (6.0%) patients in the combination therapy group versus 11 (22.4%) patients in the monotherapy group, following the 3-month treatment period. When CR was considered as response to treatment, the combination therapy group showed a higher response rate than those in the monotherapy group after 3 months of treatment (odds ratio [OR], 3.527; 95% confidence interval [CI], 1.203–6.983; p=0.011) (Table 2).

Risk factors for relapse of PMNE, 6 months following cessation of treatment, were also investigated. Among eleven patients with CR at 3 months of treatment in the monotherapy group, three (27.3%) patients showed relapse (two with PR and one with NR), whereas among 22 patients with CR at 3 months of treatment in the combination group, four (18.2%) patients showed relapse with PR at 6 months after treatment cessation. In the univariable analysis, mother

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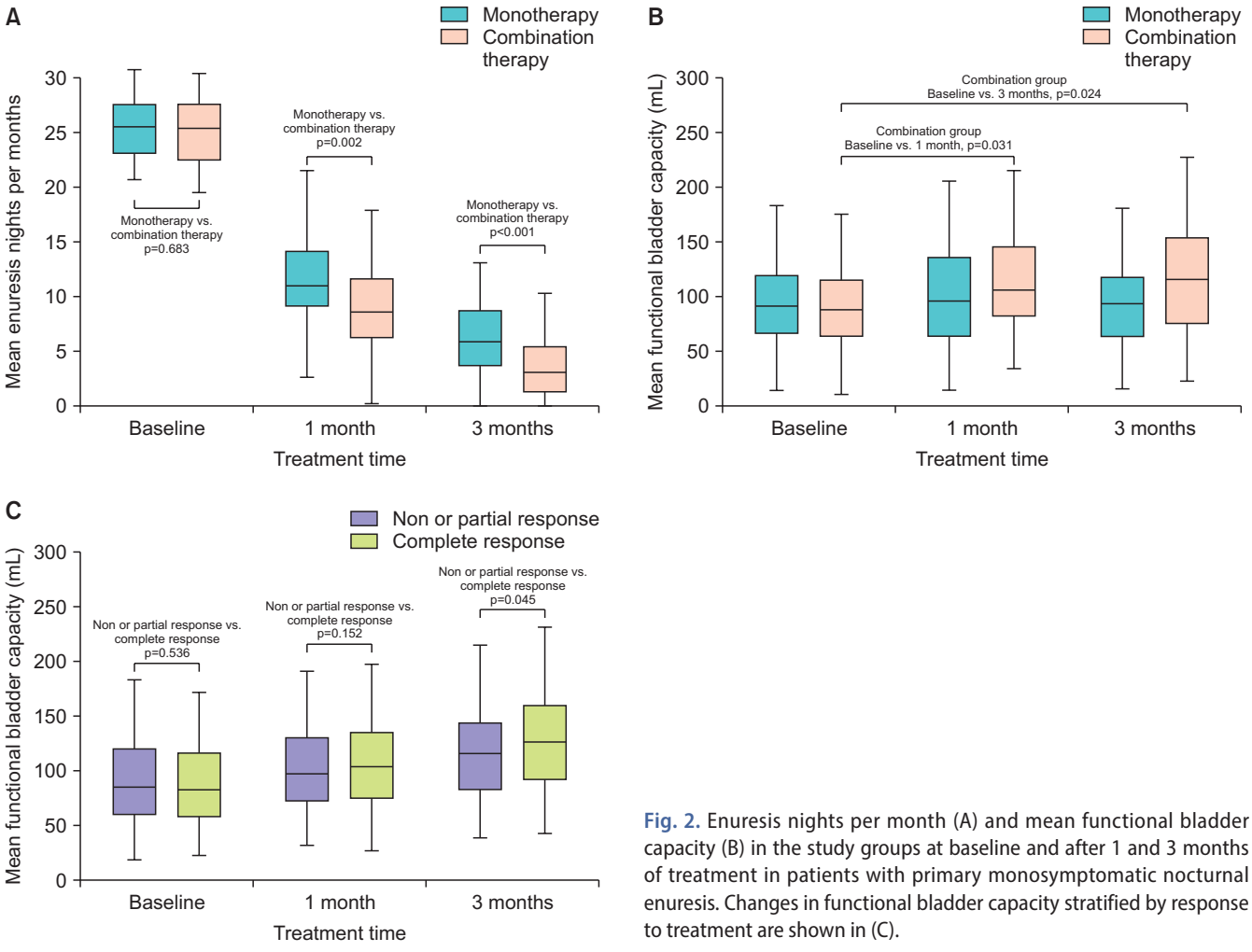

Fig. 2. Enuresis nights per month (A) and mean functional bladder capacity (B) in the study groups at baseline and after 1 and 3 months of treatment in patients with primary monosymptomatic nocturnal enuresis. Changes in functional bladder capacity stratified by response to treatment are shown in (C).

Table 2. Comparison of response rates between monotherapy with combination therapy according to the International Children's Continence Society criteria after 1 and 3 months of treatment

Time	Response to treatment	Monotherapy (n=49)	Combination therapy (n=50)	Partial response+nonresponse vs. complete response		
				OR	95% CI	p-value
1 month				2.322	1.024–12.317	0.052
	Complete response	4 (8.2)	9 (18.0)			
	Partial response	18 (36.7)	20 (40.0)			
	Nonresponse	27 (55.1)	21 (42.0)			
3 months				3.527	1.203–6.983	0.011*
	Complete response	11 (22.4)	22 (44.0)			
	Partial response	27 (55.1)	25 (50.0)			
	Nonresponse	11 (22.4)	3 (6.0)			

Values are presented as number (%).
OR, odds ratio; CI, confidence interval.
*Values are statistically significant at p<0.05.
Adjusted variables include age, sex, caregiver, obesity, family history, severity of nocturnal enuresis, and bladder capacity.

as caregiver, combination therapy, and increased bladder capacity (30% or more increase, 6 months after treatment cessation compared those at baseline) were associated with decreased relapse of PMNE (p=0.046, 0.015, and 0.021, respectively), whereas severe NE (defined as >5 wet nights/week [12]) was associated with increased relapse of PMNE (p=0.002)

Table 3. Univariable and multivariable logistic regression analysis of the factors predicting relapse 6 months after treatment cessation

Variable	B	SE	Wald	OR	95% CI	p-value
Univariable						
Age	-0.015	0.092	0.031	0.838	0.613–1.205	0.780
Sex (male)	-0.091	0.351	0.082	0.912	0.725–2.284	0.495
Mother as caregiver	-1.028	0.217	3.995	0.532	0.315–0.985	0.046*
Caregiver's age	0.021	0.086	0.028	1.285	0.703–2.137	0.812
Obesity	-0.627	0.584	1.652	1.572	0.834–5.315	0.327
Positive family history	-0.715	0.568	1.391	3.287	0.801–7.023	0.079
Severe nocturnal enuresis[a]	-1.319	0.706	6.326	2.956	1.115–6.216	0.002*
Combination therapy	1.282	0.653	6.573	0.324	0.251–0.486	0.015*
Increased bladder capacity[b]	1.289	0.686	4.352	0.385	0.187–0.905	0.021*
Multivariable						
Mother as caregiver	-0.247	0.295	4.156	0.316	0.203–1.162	0.087
Severe nocturnal enuresis[a]	-1.284	0.810	7.152	2.082	1.098–4.282	0.005*
Combination therapy	1.352	0.582	6.785	0.306	0.213–0.894	0.021*
Increased bladder capacity[b]	1.512	0.794	4.835	0.357	0.217–1.108	0.115

SE, standard error; OR, odds ratio; CI, confidence interval.
[a]:Children with more than 5 wet nights weekly.
[b]:30% or more increase in bladder capacity, 6 months after treatment cessation compared those at baseline.
*Values are statistically significant at p<0.05.

Table 4. Adverse events

Variable	Monotherapy group	Combination therapy group
Constipation	2[a]	1
Dryness of mouth	1[a]	1
Dizziness	0	0
Headache	0	0
Nausea/Vomiting	0	0
Hot flush	0	0
Palpitation	0	0
Sweating	0	0
Visual disturbance	0	0
Abdominal pain	0	0
Loss of appetite	0	0
Urinary retention	0	0
Mood disorder	0	0
Mental change	0	0

[a]:One child in monotherapy group had both mild constipation and dryness of mouth.

(Table 3). However, in the multivariable analysis, severe NE and combination therapy were independently associated with increased (OR, 2.082; 95% CI, 1.098–4.282; p=0.005) and decreased (OR, 0.306; 95% CI, 0.213–0.894; p=0.021) relapse, respectively (Table 3). No notable adverse events related to desmopressin or propiverine which require discontinuation of treatment were observed in either treatment group. All recorded adverse events related to desmopressin or propiverine were graded as 1 (asymptomatic or mild symptoms; observation only) and therefore did not require discontinuation of treatment. Detailed adverse events are shown in Table 4.

DISCUSSION

We intended in this study to evaluate the efficacy of desmopressin plus anticholinergic combination to treat PMNE as first-line treatment although it is recommended for cases of desmopressin failure in the several authoritative guidelines. In addition, we also investigated the effect of combination therapy on the FBC in children with PMNE. As a result, we have successfully found that combination therapy was associated with higher response rate with more increased FBC, and decreased relapse rate than desmopressin monotherapy.

It is well known that the use of anticholinergic drugs, together with desmopressin, in children with NE accompanied by LUTS results in a decrease in NE [13,14]. Nevertheless, there have been reports of the superior efficacy of desmopressin plus an anticholinergic agent over desmopressin monotherapy in children with NE but without LUTS or overactive bladder symptoms. Previous randomized, placebo-controlled trials have also demonstrated a significantly higher rate of decrease in the risk of a wet episode following combination therapy compared with the risk in the placebo group [1,4]. However, these randomized trials differed from our study in that patients were either a mixture of PMNE and non-monosymptomatic NE patients, or combination

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therapy was given exclusively to those children resistant to desmopressin monotherapy as a second-line therapy. Other studies have reported the efficacy of combination therapy of desmopressin and anticholinergic agents as a first-line treatment in children with pure PMNE, but these reports have limitations due to their retrospective natures [5,10,12].

Although the efficacy of combination therapy in patients with PMNE has been demonstrated, the contributing mechanism of anticholinergic agents remains unknown. The proposed mechanism for bed-wetting refractory to treatment in children with PMNE is decreased bladder capacity only after the onset of sleep at night, despite normal daytime urodynamics and FBC [13]. In addition, monotherapy non-responders with normal daytime urodynamics, and therefore initially diagnosed with PMNE, may actually have bladder instability. Alloussi et al. [15] used a video-urodynamic study to re-evaluate patients in whom monotherapy failed and detected other entities, such as terminal detrusor overactivity and phasic detrusor overactivity before micturition. Consequently, monotherapy with desmopressin alone may be ineffective because children initially classified as having PMNE may include the aforementioned patients. Indeed, earlier studies have reported treatment success rates of just 60% to 70 % (more than PR) in children, 3 months after they received desmopressin monotherapy [3,6,10]. Anticholinergic agents may play a role, particularly for a previously described subset of children with NE [13,15], who have normal expected FBC during the day and decrease FBC during the night. Anticholinergic agents are also expected to improve symptoms in patients who do not have LUTS during the day but have detrusor overactivity at night [13]. Finally, treatment success with combination therapy is based on the synergistic effect of the distinct mechanisms of the two agents: (1) desmopressin, to reduce nocturnal urine output, and (2) anticholinergic agents, to increase bladder capacity and decrease detrusor overactivity [16]. Based on this, we hypothesized that these two additive mechanisms may still be effective in children who do not have daytime LUTS and therefore, adding anticholinergics from the beginning to treat PMNE may be effective. Our results confirm the validity of these two mechanisms and the use of combination therapy as first-line treatment for PMNE. In our study, children on combination therapy showed a significant decrease in the mean number of enuresis episodes and a significant increase in FBC. Furthermore, an analysis by reclassifying patients into non or partial responders after 3 months of treatment revealed significant differences in FBC between the two groups that complete responders showed a significantly larger FBC compared with that in the non or partial responders. This suggests that the use of anticholinergic agents contributed to an increase in FBC, which eventually led to the superior efficacy compared with that in children on desmopressin monotherapy. This is further supported by previous findings that increased bladder volume or maximal voided volume during the treatment period were predictive of desmopressin response in children with NE [17,18]. In addition, according to a recent study, it can be estimated that the enuresis may be related to brain function and therefore, use of anticholinergic drugs may help improve enuresis which may be related to the effect on central nervous system [19].

Relapse rates following discontinuation of treatment are another major issue in the management of NE. Although time-dependent and dose-dependent strategies for structured withdrawal have been suggested [20,21], the exact protocol and appropriate duration remain elusive. Regardless of any withdrawal protocol, we found that combination therapy was associated with a significantly lower rate of relapse compared with that following monotherapy (18.2% vs. 27.3%, respectively), consistent with previous findings [5]. No patients in the combination therapy group showed relapse with NR whereas one patient in the monotherapy group showed relapse with NR, 6 months after treatment cessation. We also observed a novel finding: that a combination of desmopressin and propiverine was independently associated with a decreased risk of relapse when various other confounding was adjusted for the multivariable analysis.

Our study had some limitations. First, absence of placebo control in the monotherapy group not only allows for a placebo effect in the combination group but also eliminates the blinding. However, we tried to strictly control additional conditions between the two groups, such as behavior treatment and other comorbidities (e.g., constipation). Second, objective data about urodynamic studies to support our results were not included in our analysis. Third, the cost-effectiveness analysis should be further verified to justify the use of combination therapy as a first-line treatment for PMNE in the clinical practice. Fourth, including age effect on the change of bladder capacity (e.g., expected bladder capacity by age) in the analysis would have been resulted in more sophisticated conclusion. Lastly, there is concern about overtreatment in some patients who might have had satisfactory therapeutic outcomes using desmopressin only. However, in order to gain compliance from children and parents, it is important to achieve fewer wet nights within a short period. In children who achieve an acceptable outcome after desmopressin monotherapy, combination therapy may achieve a satisfactory outcome more rapidly. Also, the lower relapse rate of combination therapy compared with that of

monotherapy can counterbalance concerns around overtreatment. To the best of our knowledge, our study represents the first report on the efficacy of combination therapy as a first-line treatment for children with PMNE, based on the results from a prospective randomized controlled trial with a large number of patients and a relatively long follow-up period. It is specifically noteworthy that our results demonstrate the novel finding of significantly fewer episodes of wet nights, concomitant with increased bladder capacity, throughout the treatment period in the combination therapy group. Moreover, it should be emphasized that all our patients had completed FVC and elimination records and were therefore highly selected to avoid any confounding effects from LUTS or overactive bladder symptoms. Further placebo-controlled trials or detailed subgroup analyses, together with our findings, will contribute to advances in first-line treatments for PMNE.

CONCLUSIONS

Combination therapy with desmopressin plus anticholinergic agent as the first-line treatment for PMNE produced a higher response rate and lower relapse rate than desmopressin monotherapy. This superior outcome following combination therapy probably arises because anticholinergic agents increase bladder capacity. Therefore, anticholinergic drugs may be considered at the start when treating PMNE.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Myungsun Shim and Cheol Young Oh. Data acquisition: Myungsun Shim, Woo Jin Bang, Cheol Young Oh, and Jin Seon Cho. Statistical analysis: Myungsun Shim. Data analysis and interpretation: Myungsun Shim. Drafting of the manuscript: Myungsun Shim. Critical revision of the manuscript: Myungsun Shim, Cheol Young Oh, and Min Jae Kang. Obtaining funding: Myungsun Shim. Administrative, technical, or material support: Myungsun Shim and Cheol Young Oh. Supervision: Min Jae Kang and Cheol Young Oh, Approval of the final manuscript: Cheol Young Oh.

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