RESEARCH PAPER

Desmopressin Plus Tolterodine vs Desmopressin Plus Indomethacin for Refractory Pediatric Enuresis: An Open-label Randomized Controlled Trial

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Objective: To compare the efficacy of desmopressin plus tolterodine (D+T) with desmopressin plus indomethacin (D+I) for treating enuresis in children.

Design: Open-label randomized controlled trial.

Setting: Bandar Abbas Children's Hospital, a tertiary care children's hospital in Iran, from March 21, 2018, to March 21, 2019.

Participants: 40 children older than five years with monosymptomatic and non-monosymptomatic primary enuresis resistant to desmopressin monotherapy.

Intervention: Patients were randomized to receive either D+T (60 µg sublingual desmopressin and 2 mg tolterodine) or D+I (60 µg sublingual desmopressin and 50 mg indomethacin) every night before bedtime for five months.

Outcome: Reduction in the frequency of enuresis was evaluated at one, three, and five months, and response to treatment at five months. Drug reactions and complications were also noted.

Results: After adjustment for age, consistent incontinence from toilet training, and non-monosymptomatic enuresis, D+T was significantly more efficacious than D+I; mean (SD) percent in nocturnal enuresis reduction at 1 [58.86 (7.27)% vs 31.18 (3.85) %; *P*<0.001], 3 [69.78 (5.99)% vs 38.56 (3.31)%; *P*<0.000], and 5 [84.84(6.21)% vs 39.14 (3.63)%; *P*<0.001] months showing a large effect. At 5 months, complete response to treatment was only observed with D+T, while treatment failure was significantly higher with D+I (50% vs 20%; *P*=0.047). None of the patients in either group developed cutaneous drug reactions or central nervous system symptoms.

Conclusion: Desmopressin plus tolterodine appears to be superior to desmopressin plus indomethacin for treating pediatric enuresis resistant to desmopressin.

Keywords: *Adverse effect, Combination therapy, Management, Outcome.*

Trial Registration: Iranian Registry of Clinical Trials: IRCT20210613051564N1

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Enuresis, defined as bedwetting in children aged 5 years and above, is seen in around 15-20% of five-year-old children, 6.4-10.3% of seven-year-olds and 0.5-2.3% of adults, with a 15% annual spontaneous resolution rate [1,2]. Nocturnal enuresis (NE) is defined as bedwetting at night for at least three consecutive months in children aged >5 years [3]. Psychological and social issues, rather than somatic problem, are the main reasons for treating children with enuresis [3].

Desmopressin, a selective vasopressin V2 receptor agonist, is the first-line medical treatment for enuresis [4]. Generally, desmopressin is well tolerated, with hyponatremia being a rare but serious side effect [5]. The International Children's Continence Society (ICCS) recommends combination therapy when the first-line monotherapy fails [6]. Anticholinergics like tolterodine, in combination with desmopressin have been shown to be effective for treating NE [7,8]. Its side effects include dry mouth, dry eyes, constipation, urinary tract infection, hypertension, headache, blurred vision, and drowsiness [9]. Further, evidence suggests overproduction of prostaglandin E2 during the night in some children with enuresis [10]. Therefore, cyclooxygenase inhibitors such as indomethacin, which have been demonstrated to possess antidiuretic properties, have been used for treating patients with enuresis [11]. The side effects of indomethacin range from mild, such as nausea, to severe, such as increased bleeding tendency [12]. In this study, we aimed to compare the effects of desmopressin plus tolterodine with desmopressin plus indomethacin for treating children with enuresis.

METHODS

This open-label randomized controlled trial, registered at the Iranian Registry of Clinical Trials, included children over five years of age with monosymptomatic and non-monosymptomatic (simultaneous daytime lower urinary tract symptoms, such as daytime incontinence, urgency, voiding difficulties, and abnormally low or high daytime voiding frequency) primary enuresis [13]. Ethics approval was taken from the ethics committee of our university.

Monosymptomatic enuresis was diagnosed after ruling out secondary causes of enuresis, including anatomic abnormalities of the urinary tract, trauma, constipation, urinary tract infection, diabetes insipidus, excessive water intake, spinal cord disorders, hypercalciuria, diabetes mellitus, and adenoid disorders. The diagnosis was made by a pediatric nephrologist, at a tertiary care children's hospital in Iran, from March 21, 2018, to March 21, 2019. The children were included when they were resis-tant to monotherapy with desmopressin, defined as <50% reduction in the number of wet nights with incremental doses of 120 to 240 µg [14], no response to alarm therapy, and normal uroflowmetry and residual volume.

The sample size was calculated as 20 patients in each group using data from a pilot study (10 samples in each group) with mean nocturnal enuresis reduction after 15 days of 16.69% (10.91%) for the desmopressin + indomethacin (D+I) group and 28.37% (13.45%) for the desmopressin + tolterodine (D+T) group, α=0.05 and β=0.2, and by taking into account a 10% loss to follow-up.

After taking written informed consent from the parents/guardians of the patients, demographic and clinical details including history of consistent incontinence from the age of toilet training and family history of enuresis were recorded. The children were randomized into two groups using a randomization table generated by the Random Allocation software, version 1.0 [15]. Children in the D+T group received a 60 µg sublingual desmopressin tablet and a 2 mg tolterodine tablet every night before bedtime, while children in the D+I group received a 60 µg sublingual desmopressin tablet and two 25 mg (50 mg) indomethacin capsules every night before bedtime. Both groups received medications for five months. Concurrent use of other medications was noted. Compliance with the treatments was evaluated from their parents.

The primary outcome was a reduction in the frequency of nocturnal enuresis, one, three, and five months after the initiation of treatment, assessed by a 24-hour frequency chart filled in by the parents. To compare the response to medication at the end of the study period (at 5 months), we used the definition of the Standardization Committee of

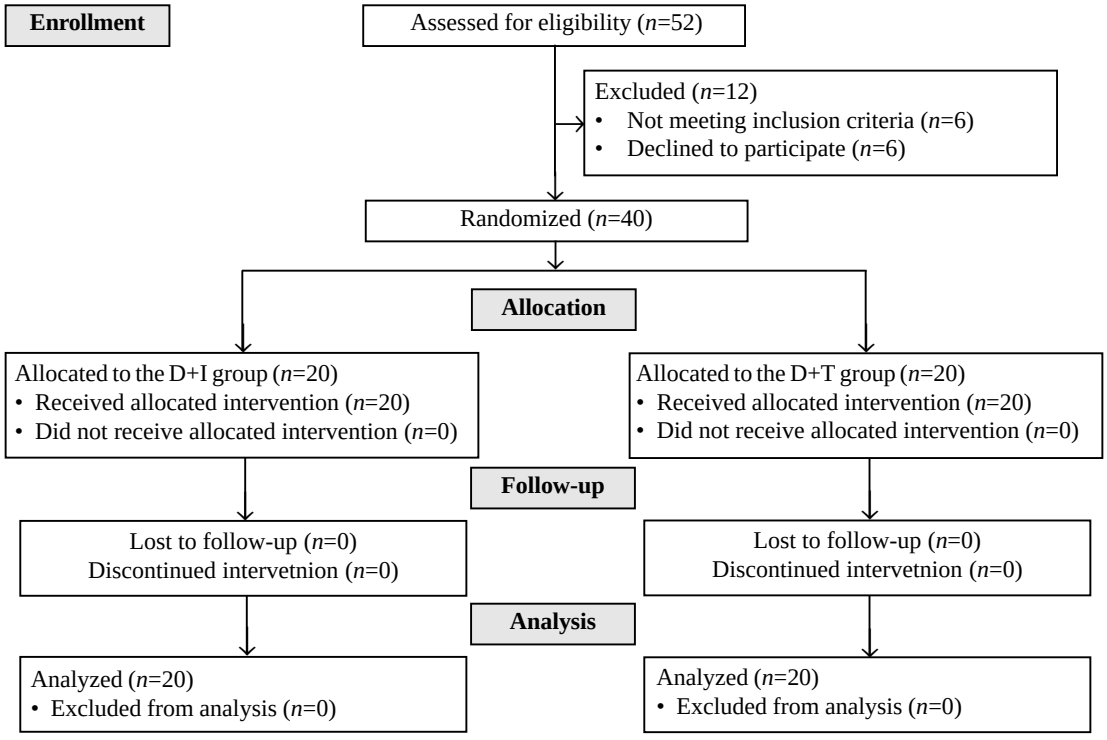

Fig. 1 CONSORT flow diagram for the study.

Table I Baseline Demographic Characteristics of Children With Nocturnal Enuresis in the Two Treatment Groups

Variables	*Desmopressin+ indomethacin (n=20)*	*Desmopressin+ tolterodine (n=20)*
Age (y)[a]	8.56 (0.98)	9.05 (2.21)
Male sex	9 (45)	9 (45)
Family history of enuresis	11 (55)	10 (50)
Incontinence since toilet training	19 (95)	15 (75)
Non-monosymptomatic enuresis	10 (50)	8 (40)

All values are no. (%) or [a]mean (SD).

Table II Response of Nocturnal Enuresis in the Two Study Groups at Various Time Points

Response	*Desmopressin+ indomethacin (n=20)*	*Desmopressin+ tolterodine (n=20)*	*P value*
Frequency of nocturnal enuresis at each month[a]			
One month	31.18 (3.85)	58.86 (7.27)	<0.001
Three month	38.56 (3.31)	69.78 (5.99)	<0.001
Five month	39.14 (3.63)	84.84 (6.21)	<0.001
Response to treatment at 5 months[b]			
Failure	10 (50)	4 (20)	0.047
Partial	10 (50)	6 (30)	0.197
Complete	0	10 (50)	<0.001

[a]Values are % nocturnal enuresis reduction in mean (SD) or [b]no. (%).

the ICCS [16] as follows: *i*) Complete response to treatment: ≥90% reduction in the frequency of enuresis per week; *ii*) Partial response to treatment: 50-89% reduction in the frequency of enuresis per week; and *iii*) Failed response: <50% reduction in the frequency of enuresis per week. The incidence of cutaneous drug reactions, and gastrointestinal or central nervous symptoms were recorded.

Statistical analysis: The Stata software (version 14.2, StataCorp LLC) was used. Due to the non-normal distribution of nocturnal enuresis reduction, a logarithmic transformation was performed for analysis, and then data were retransformed to be reported in the tables. Accordingly, the ANOVA/ANCOVA test was used to evaluate the effect of interventions on this parameter at different time points, with age as covariance, and consistent incontinence since toilet training and non-monosymptomatic enuresis as factors. Standardized mean difference (SMD) was calculated for adjusted means in each model using Glass delta. SMD interpretation was as follows: ≤0.19, trivial; 0.20-0.49, small effect; 0.50-0.79, medium effect; and ≥0.80, large effect. Eta^2 was interpreted based on the following: <0.010, trivial; 0.010-0.059, small effect; 0.060-0.139, medium effect; and ≥0.140, large effect. The chi-square test was used to compare categorical data between groups, and risk ratios were reported as effect size with the following interpretations: 0-0.81, trivial effect; 0.53-0.82, small effect; 0.32-0.54, medium effect; and ≥0.33, large effect. *P* values <0.05 were regarded as statistically significant.

RESULTS

Of the 52 children assessed for eligibility, a total of 40 patients were randomized into two groups (**Fig. 1**). **Table I** shows the baseline characteristics of the patients in both groups. None of the patients were concurrently on medications other than the study medications. D+T was significantly more efficacious than D+I in nocturnal enuresis reduction at one, three, and five months (**Table II**). At five months, complete response to treatment was only observed with D+T in 50% of children, while treatment failure was significantly higher with D+I [10 (50%) in D+I vs 4 (20%) in D+T group; *P*=0.47]. The proportion of children with partial response was not significantly different between the groups [10 (50%) in D+I vs 6 (30%) in D+T group; *P*= 0.197] (**Table II**).

After adjustment for age, consistent incontinence since toilet training, and non-monosymptomatic enuresis, D+T was still significantly more efficacious than D+I in nocturnal enuresis reduction at one, three, and five months (**Web Table I**).

None of the patients in either group developed cutaneous drug reactions or central nervous symptoms. All patients had complete compliance with the treatments.

DISCUSSION

In the current study, we found a significantly higher reduction in the frequency of nocturnal enuresis in children of the D+T group compared to those taking D+I, one month after the initiation of treatment, and at 3- and 5-month follow-ups. We also found that complete response to treatment was significantly higher with D+T, at the end of the study period. This suggests that desmopressin plus tolterodine combination therapy can be more successful than desmopressin plus indomethacin in treating pediatric patients resistant to desmopressin monotherapy. Although, there are no published trials contrasting D+T and D+I for the treatment of refractory nocturnal enuresis, these two combination therapies have both been evaluated against placebo in earlier research. Austin, et al. [8] demonstrated that a one-month combined treatment regimen of desmopressin and tolterodine reduced the mean number of wet episodes more effectively than desmopressin and placebo. However, the D+T group in our trial received a sub-

stantially lower total dosage of tolterodine (2 mg) than used by Austin, et al. [8], demonstrating that tolterodine at lower doses can still be just as effective. Likewise, Rashed, et al. [17] compared D+T with desmopressin plus placebo and showed that this combination therapy was superior in terms of treatment response. Their study's tolterodine dosage was comparable to ours. Kamperis, et al. [11] compared desmopressin plus indomethacin with desmopressin plus placebo to treat monosymptomatic nocturnal enuresis. They found that indomethacin significantly reduced nocturnal urine output compared to placebo. The number of dry nights; however, did not differ across groups [11].

Explanations for why children with nocturnal enuresis do not respond to desmopressin as the first-line treatment include patient compliance, variability in pharmacodynamics and pharmacokinetics, dietary variables, the timing of desmopressin administration, and hydration state [18,19]. Some patients who are resistant to desmopressin show bladder instability [20], and almost 70% of patients with bladder overactivity suffer from nocturnal enuresis [21], with decreased nocturnal functional bladder capacity seen commonly in refractory nocturnal enuresis [22]. These results and reports imply that desmopressin plus anticholinergic combination therapy may improve nocturnal enuresis [8,17], though additional research is required to identify the ideal anticholinergic drug and its dosage. On the other hand, nonsteroidal anti-inflammatory drugs (NSAIDs) have been claimed to have antidiuretic properties, and may be used in children who do not respond to conventional therapeutic approaches. Due to the inclusion of unselected populations, studies using different NSAIDS have yielded inconsistent results [23-25].

Tolterodine is a competitive antagonist of acetylcholine at postganglionic muscarinic receptors.Therefore, by acting as a muscle relaxant, tolterodine can increase the bladder's capacity to hold urine [26]. On the other hand, indomethacin appears to exert its antidiuretic effect through anti-natriuretic properties, reduction in urea, and overall osmotic clearance. Moreover, by acting on the nervous system, tolterodine appears to have more stable effects, while indomethacin functions might be mediated under accompanying inflammatory conditions in patients with nocturnal enuresis.

The strength of our study was its randomized controlled trial design. Nonetheless, including a placebo group could have added merit to this study. One limitation was that some of our patients in both groups were non-monosymptomatic. Moreover, bladder capacity can affect outcomes, especially in patients taking anticholinergic agents, and we did not compare our patients in this regard. Also, the urine output which may be an indicator of drug efficacy [11], was not assessed in our patients. Furthermore, the small sample size of this study can limit the generalizability of our findings. Finally, long-term outcomes, including relapse, continued success, and complete success [14] were not evaluated in this study.

Desmopressin plus tolterodine was superior to desmopressin plus indomethacin for the treatment of mono- and non-monosymptomatic nocturnal enuresis in this study. Further studies with a placebo arm and a larger sample size are required to confirm our findings.

Ethics clearance: IEC, Hormozgan University of Medical Sciences; No. IR.HUMS.REC.1397.070 dated May 13, 2018.
Contributors: ME: conceptualization and study validation, writing and reviewing; SEM: implementation and supervision; GZ: data analysis and interpretation. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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Web Table I Comparison of Effects on Nocturnal Enuresis Reduction Between the Groups (Adjusted Analysis)

Time	*Desmopressin + indomethacin (n=20)*	*Desmopressin + tolterodine (n=20)*	*SMD (95%CI)*	*P-value**
At one month				
Model 1	31.52 (24.78, 40.09)	58.23 (45.78, 74.30)	5.30 (3.51, 7.08)	0.001
Model 2	30.45 (23.91, 38.79)	60.27 (47.32, 76.77)	5.92 (3.94, 7.88)	<0.001
Model 3	30.33 (28.90, 38.50)	60.51 (47.67, 76.80)	6.00 (4.00, 7.98)	<0.001
At three months				
Model 1	38.66 (32.62, 45.83)	69.58 (58.70, 82.48)	6.36 (4.25, 8.45)	<0.001
Model 2	37.91 (31.90, 45.05)	70.98 (59.73, 84.36)	6.79 (4.55, 9.01)	<0.001
Model 3	37.87 (31.80, 45.09)	71.06 (59.67, 84.61)	6.81 (4.57, 9.04)	<0.001
At five months				
Model 1	39.25 (32.62, 47.22)	84.69 (73.19, 98.01)	9.47 (6.41, 12.51)	<0.001
Model 2	39.25 (32.41, 47.52)	84.69 (72.85, 98.45)	9.45 (6.40, 12.48)	<0.001
Model 3	39.45 (32.57, 47.79)	84.42 (72.61, 98.17)	9.35 (6.33, 12.36)	<0.001

SMD: standardized mean difference; All values are % nocturnal enuresis reduction, mean (confidence interval of mean). Model 1: adjusted for age; Model 2: adjusted for age and consistent incontinence since toilet training; Model 3: adjusted for age, consistent incontinence since toilet training, and non-monosymptomatic enuresis.