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COMBINATION TREATMENT WITH SOLIFENACIN PLUS DESMOPRESSIN FOR CHILDREN WITH PERSISTNET NOCTURNAL INCONTINENCE WHICH LASTS AFTER OBTAINNING COMPLETE CURE OF URGE URINARY INCONTNENCE

Aims of study: Overactive bladder (OAB) symptoms such as urgency, increased daytime frequency and urge urinary incontinence are common in childhood. Children with OAB often suffer from concomitant nocturnal incontinence during sleep. Whereas urotherapy and antimuscarinic agents are thought to be effective for the OAB symptoms, concomitant nocturnal incontinence is usually refractory for those treatments and often persists after obtainning complete cure of urge urinary incontnence. However, therapeutic strategies for the persistent nocturnal incontinence in children with OAB have not been well studied. Therefore, we elucidated, in a prospective study, the efficacy and safety of the combination treatment with oral antimuscarinic solifenacin plus desmopressin for children with refractory nocturnal incontinence which lasts after complete cure of urge urinary incontnence.

Materials and methods: This study included 52 patients with primary nocturnal incontinence (nocturnal incontinence episodes >/= 8 times during 14 days) which lasts after obtaining complete cure of urge urinary incontnence. Before this study, all patient had prevously suffered from urge urinary incontinence during the day and they recovered urge urinary incontinence by taking the standard urotherapy included timed voiding and management of bowel movement and/or anticholinergic treatment at our outpatient department. The nocturnal incontinence which had been concomitnet with urge urinary incontinence was not responsive to the previous treatment for urge urinary incontinence. For patients who were highly motivated to undergo additional treatment for the persistent nocturnal incontinence, three therapeutic options were informed. Exclusion criteria were neurourologic disease, active urinary tract infections, nocturnal polyuria, attention deficit hyperactivity disorder/learning disorders, under the age of seven years-old, monosymptomatic nocturnal enuresis. The patients were divided into three groups. In alarm group (n=16), the patients were given enuretic alarm therapy alone. In desmopressin group (n=25), the patients were given intranasal desmopressin at bedtime, as a single dose of 10-30 μg. In combination group (n=21), the patients were given once daily oral solifenacin 2.5mg and intranasal desmopressin (10-30 μg) at bedtime. The primary endpoints were theraputic efficacy of each treatment for persistent nocturnal incontinence. The number of wet nights, as well as the appearance of nocturia, and total nocturnal urine production during sleep was investigated before and during the last 14 days of each treatment. Nocturnal urine production was calculated by diaper weight plus the first morning micturition volume. The efficacy of each treatment was assessed at 8 to 12 weeks, according to the definition of clinical outcome conformed to the International Children's Continence Society [1]. The patients were defined as full response (complete dry), response (90 to 99% reduction in wet nights), partial response (50 to 90% reduction). Patients who showed more than 50% decrease in wet nights during each treatment were defined as responders. All children and families gave full informed consent. The data were analysed statistically using the non-parametric Mann-Whitney U test.

Results: A total of 62 patients who underwent additional treatment for persistnet nocturnal incontinence which lasts after obtainning complete cure of urge urinary incontnence were enrolled in the study. Two girls in alarm group and one boy in desmopressin group were excluded due to their poor compliance with the treatment. One girl in combination treatment withdrew due to the adverse events of low-grade headach. A total of 58 patients (40 boys and 18 girls) between 6 and 14 years (mean age 9.2 year) were evaluated. The three groups were matched for age, pre-treatment number of nocturnal incontinence and nocturnal urine production during sleep. Nineteen percent (11) of patients reported >/=1 adverse events during the study. The most frequent adverse events were nasopharyngitis (7.7%), constipatin (5.2%), headache (3.4%), and abdominal pain (1.7%). One (1.7%) patient withdrew, however, almost were mild. Full respose, response and parital respons were found in 0, 7.1 and 14.3% of alarm group, and 0, 25.0 and 16.7% of desmopressin group, respectively. However, full respose, response and parital respons were found in 10.0, 20.0 and 25.0% of combination group, respectively. Combination threatment and desmopressin treatment offered statistically more preferable relief of persitent nocturnal incontinence than enuresis alarm.

	Alarm (n=14)	Desmopressin (n=24)	Combination (n=20)
Age (years)	10.4±1.8 (8-13)	9.4±1.6 (7-12)	9.1±1.9 (6-14)
Treatment period (weeks)	11.7±1.0 (9-12)	8.2±0.8 (8-12)	13.7±1.8 (8-17)
Nocturnal urine production Pre-treatment (ml)	196.4±67.2 (110-320)	208.7±80.0 (130-380)	217.4±67.2 (110-320)
Nocturnal urine production Post-treatment (ml)	189.4±87.4 (120-340)	171.0±68.2 (100-260)	177.4±77.4 (100-270)
Responders, % (n)	21.4% (3)	41.7% (10)	55.0% (11)

Interpretation of results: Our results give the suspection that both functional small bladder capacity and persistent detrusor overactivity during sleep are the reasons for persistent nocturnal incontinence which lasts after gaining daytime urinary continence. Nocturnal incontinence may last wiht mautifactorial pathogenetic mechanisms and combination treatment might be

useful by reducing the onset of idiopathic detrusor overactivity and reducing urine production during sleep, resulting in better relief of nocturnal incontinence than desmopressin alone.

Concluding message: For patients who sufferd from persistent nocturnal incontinence which lasts after obtainning complete cure of urge urinary incontnence, combination treatment with solifenacin plus desmopressin could be safe, and more effective therapuitic option than desmopressin and enuresis alarm.

References

1. 1. Nevéus T, Gontard A, et al.: The standardization of terminology of lower urinary tract function in children and adolescents: report from the standardization committee on the International Children's Continence Society. J Urol, 176: 314-324, 2006.

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Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**No**
Is this a Randomised Controlled Trial (RCT)?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**No**
This study did not require eithics committee approval because	**Our study is a small and pilot study.**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**