

The Efficacy of Enuresis Alarm Treatment in Pharmacotherapy-Resistant Nocturnal Enuresis

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OBJECTIVES	To assess the efficacy of enuresis alarm (EA) treatment in pharmacotherapy-resistant nocturnal enuresis (PRNE).
MATERIAL AND METHODS	A retrospective study was performed in children who received EA treatment as a form of combination treatment for PRNE from June 1999 to December 2007. The children included 54 monosymptomatic nocturnal enuresis (MNE) children who had partial response or nonresponse to desmopressin (group 1), 25 nonmonosymptomatic nocturnal enuresis (NMNE) children who had partial response or nonresponse to extended release oxybutynin plus desmopressin (group 2), and 21 MNE or NMNE children who relapsed after responding fully to first-line pharmacotherapy (group 3). EA treatment outcomes were determined as outlined by the International Children's Continence Society Standardisation Committee.
RESULTS	Overall, 50% and 53.7%, 40%, and 52.4% of children in groups 1, 2, and 3, respectively, responded fully to EA treatment (no significant differences). In groups 1 and 2, 54.4% (31/57) of the partial responders and 36.4% (8/22) of the nonresponders showed full response (FR) after EA treatment was initiated. Of the children with small bladder capacities, 56.7% showed FR. Of the full responders in each group, 60.7%, 88.9%, and 54.5% of groups 1, 2, and 3, respectively, did not have relapse 6 months after cessation of treatment.
CONCLUSIONS	Overall, half of the total population achieved FR, and continued success was observed in more than half of full responders irrespective of the groups. Thus, adding EA treatment to pharmacotherapy is an effective second-line therapeutic strategy for children with PRNE. UROLOGY 77: 200–204, 2011. © 2011 Elsevier Inc.

Nocturnal enuresis (NE) is categorized as monosymptomatic (MNE) or nonmonosymptomatic (NMNE) based on whether daytime lower urinary tract symptoms (LUTS) are absent or present.¹ Current treatment options for MNE include desmopressin and enuresis alarm (EA), and their efficacy depends on the relationship between nocturnal bladder capacity and nocturnal urine output.² In children with NMNE, anticholinergics have been used to treat the daytime LUTS caused by detrusor overactivity. However, little is known about which therapeutic strategies would be most effective for MNE and NMNE patients who do not respond fully to primary pharmacotherapy or children with had relapse of NE. To assess the therapeutic efficacy

of EA in PRNE, we used EA as a second-line treatment for these selected groups.

MATERIALS AND METHODS

A retrospective analysis was performed in 127 enuretic children who received EA treatment as a form of combination treatment for pharmacotherapy-resistant NE (PRNE) from June 1999 to December 2007. PRNE was defined as MNE or NMNE that did not respond fully to primary pharmacotherapy or relapsed after cessation of primary pharmacotherapy. Any children with neuropathic bladder, spinal dysraphism, anatomical abnormalities, or known history of previous EA treatment were excluded. A detailed history, including LUTS questionnaire, physical examination, and a 3-day bladder diary were obtained from all patients before starting primary pharmacotherapy. The maximum voided volume (MVV) was recorded by a 3-day bladder diary, and the expected bladder capacity (EBC), as determined by using the formula $[30 + (\text{age in years} \times 30)]$, were calculated. After enuretic children were categorized by LUTS questionnaire and a 3-day bladder diary, they were provided with primary pharmacotherapy, namely desmopressin for MNE or oxybutynin combined with desmopressin for NMNE. Children included in this study received combination treatment using a body-worn alarm device (Malem Medical, Nottingham, UK)

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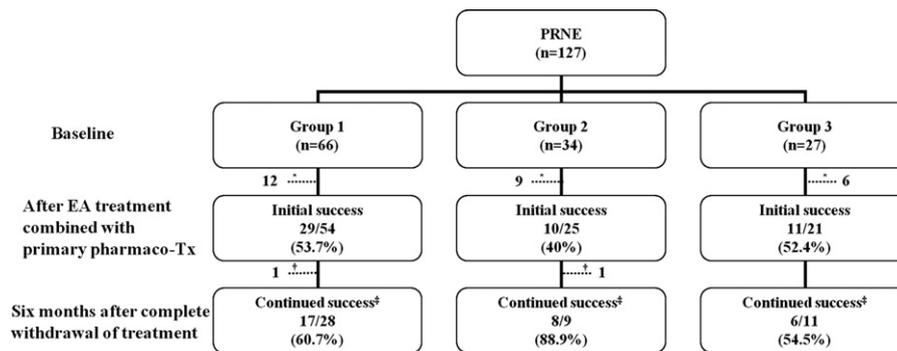


Figure 1. Flow diagram of study. Tx = treatment. *Defaulted from treatment. †Defaulted follow-up. ‡Data in full responders to EA combined with pharmacotherapy.

Table 1. Patients' characteristics

Characteristic	Group 1	Group 2	Group 3
Mean \pm SD age (range)	8.8 \pm 2.0 (5–13)	7.6 \pm 1.8 (6–11)	8.9 \pm 2.0 (6–13)
No. of patients	54	25	21
Male/female ratio	39/15	18/7	13/8
Mean duration of pharmacotherapy in weeks (range)	19 (12–36)	24 (16–43)	23 (12–40)
Mean No. of wet nights/4 weeks before pharmacotherapy (range)	23 (12–28)	27 (12–28)	24 (12–28)
Mean No. of wet nights/4 weeks before EA Tx (range)	9 (3–28)	10 (4–18)	7 (3–16)
Mean duration of added EA Tx in weeks (range)	18 (10–35)	17 (12–28)	17 (12–24)
No. small bladder capacity* (%)	33 (61.1)	17 (68.0)	10 (47.6)

Nonresponse defined as a 0%–49% decrease of wet nights. Partial response defined as a 50%–89% decrease of wet nights; Tx = treatment.

* <65% of MVV/volume expected for age.

with primary pharmacotherapy. Before being treated with an EA, all children were advised to empty their bladder and restrict fluid and fruit intake before going to bed. The study population was subdivided into 3 groups: group 1 ($n = 66$) consisted of MNE children who were partial or nonresponders to desmopressin, of which dose was started at 0.2 mg daily and increased to 0.4 mg daily; group 2 ($n = 34$) consisted of NMNE children who were partial or nonresponders to extended-release oxybutynin, started at 5 mg daily and increased to 15 mg daily, combined with desmopressin; and group 3 ($n = 27$) consisted of 23 MNE and 4 NMNE children who relapsed after making a full response (FR) to first-line pharmacotherapy. Depending on the response to the EA treatment, the pharmacotherapy dose was gradually tapered. EA treatment was discontinued when the child achieved FR for the previous 4 weeks of treatment. The number of dry nights was assessed every 4 weeks during the EA treatment and every 12 weeks after the achievement of FR. The response to treatment was assessed on the basis of the Standardization Committee of the ICCS.³ A relapse was defined as more than one wetting episode monthly, whereas continued success was defined as the absence of relapses for 6 months after all treatments were ceased. All statistical analyses were performed using a commercially available statistical program (SPSS, version 13.0, SPSS, Inc., Chicago, IL). Probability values less than .05 were considered statistically significant.

RESULTS

Of the total population, 12, 9, and 6 children had inconsistent or short-term use (<8 weeks) of the alarm device in groups 1, 2, and 3, respectively. They were excluded from the study. A flow diagram of the study is shown in

Figure 1, and the characteristics of the population are presented in Table 1. Among the 100 enuretic children included in this study, 50 (50%) exhibited FR when EA treatment was added to pharmacotherapy. After EA treatment was added, groups 1, 2, and 3 exhibited FR rates of 53.7%, 40%, and 52.4%, respectively. These differences were not statistically significant ($P = .798$). Figure 2 demonstrated the response of children in groups 1 and 2 to EA treatment to ongoing pharmacotherapy. In group 1, 26 (61.9%) of 42 children with PR to primary pharmacotherapy attained FR, and 9 (75%) of 12 children with nonresponse (NR) showed FR in 3 and PR in 6 after EA treatment was added (Fig. 2A). In group 2, 5 (33.3%) of 15 children with PR to primary pharmacotherapy achieved FR, and 9 (90%) of 10 children with NR showed FR in 5 and PR in 4 after EA treatment was added (Fig. 2B). Analyzed according to the response to the primary pharmacotherapy, 31 (54.4%) of the 57 partial responders and 8 (36.4%) of the 22 nonresponders achieved FR ($P = .006$). Of the 21 relapsed children, 11 exhibited FR and the remainder showed PR after EA treatment was added.

In terms of bladder capacity, there were 60 children who had a small bladder capacity (<65% of maximum voided volume/volume expected for age) and 40 with a normal bladder capacity (Table 1). Of the 60 children with a small bladder capacity, 34 (56.7%) showed FR after EA treatment, whereas 16 (40%) of the children with normal bladder capacity exhibited FR (Table 2).

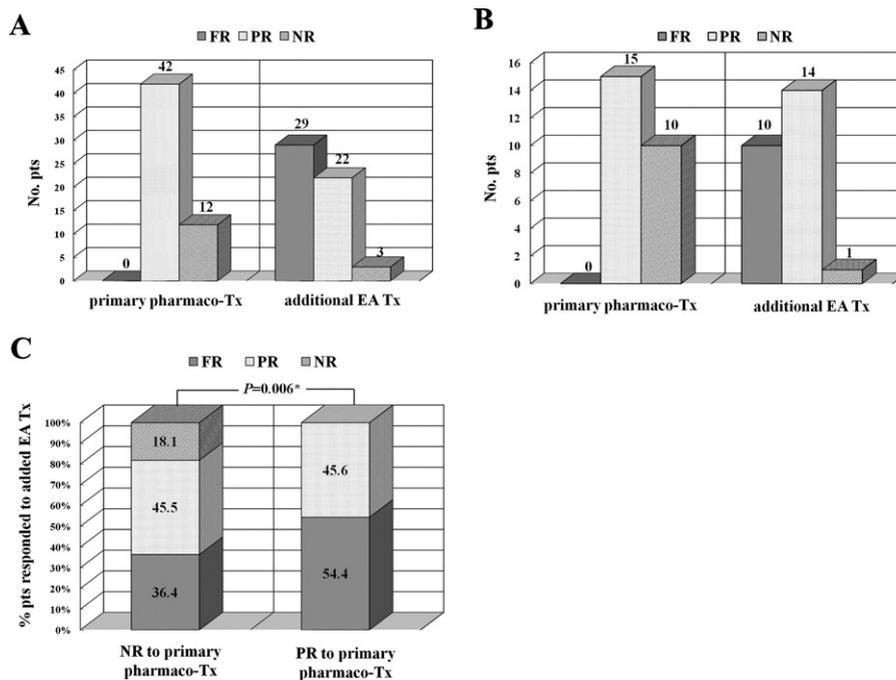


Figure 2. Response to adding EA treatment to ongoing pharmacotherapy by children with pharmacotherapy-resistant NE. **(A)** Children with MNE (n = 54). **(B)** Children with NMNE (n = 25). **(C)** Children with NR (n = 22) or PR (n = 57) to primary pharmacotherapy in groups 1 and 2 (n = 79). Tx = treatment, FR = full response, PR = partial response, NR = nonresponse. *Compared by Fisher's exact test.

Table 2. Outcomes of added EA treatment according to the bladder capacity

	Bladder Capacity		P*
	Small†	Normal	
Response to added EA Tx (%)			
FR	34 (56.7)	16 (40.0)	.247
PR	24 (40.0)	21 (52.5)	
NR	2 (3.3)	3 (7.5)	

Tx = treatment.

* Compared by Fisher's exact test.

† <65% of maximum voided volume/volume expected for age.

However, this difference did not achieve statistical significance ($P = .247$). Those who were lost to follow-up after withdrawal of EA treatment were 1, 1, and 0 in groups 1, 2, and 3, respectively. Among 48 full responders to EA treatment combined with pharmacotherapy, 31 (64.6%) continued to be dry after withdrawal of treatment. Groups 1, 2, and 3 showed the continued success rates of 60.7%, 88.9%, and 54.5%, respectively.

COMMENT

NE is a heterogeneous disorder that is caused by one or more pathophysiological mechanisms that can result in clinical manifestations that vary in severity. The occurrence of NE seems to be determined by 3 main factors that may interact with each other: nocturnal polyuria, nocturnal bladder reservoir function, and the arousal response to bladder fullness during sleep.⁴ The complex nature of NE pathophysiology means that treatment

should be shaped specifically to target the underlying dysfunction of each patient.

To date, several studies have examined NE that is refractory to primary therapy.⁵⁻⁷ The study of Yeung et al⁵ revealed that children with refractory MNE often have various types of bladder dysfunction. Another study by Yeung et al⁶ then revealed that severe NE that was refractory to treatment was driven by a reduced nocturnal functional bladder capacity rather than nocturnal polyuria. Kamperis et al⁷ subsequently suggested that nocturnal polyuria that resulted from higher urinary prostaglandin E₂ levels was associated with NE that was refractory to desmopressin treatment.

The underlying mechanism by which EA treatment improves NE may involve the ability of the central nervous system to inhibit the micturition reflex and increase the nocturnal bladder capacity.⁸ EA treatment is the most clinically effective measure against NE because its cure rate is higher than that of other anti-NE measures. Jensen and Kristensen⁹ have reported that EA treatment may be particularly effective for the most severe cases of NE, which suggests that new reflexes are more rapidly trained when a child has a high frequency of wet nights. The study by Butler et al¹⁰ showed that EA facilitates a child becoming dry through increased urine concentration and thus reduced urine volume. They offered an insight into possible mechanisms whereby the EA enables children to become dry at night.

In the case of children with NE who do not respond to primary therapy, it has been recommended that a combination of different modalities be used next. However,

although it has been shown that enuretic children with larger nocturnal urine output are likely to achieve dryness when desmopressin is added to EA treatment,¹¹ studies examining the outcomes of combination therapy using pharmacotherapy and EA have yielded conflicting reports.¹²⁻¹⁴

There are also very few studies that have examined the efficacy of EA treatment for NMNE or relapsed NE. Van Leerdam et al¹⁵ showed that children with day- and nighttime wetting could be primarily treated by using EA, with 67% of such children showing dryness at night and 42% becoming dry during the daytime. Recently, 2 studies showed that when a large number of patients who were initially diagnosed with MNE were thoroughly investigated, they had some daytime LUTS.^{16,17} This finding reaffirms the heterogeneity of NE, which is a result of the variety of pathophysiological mechanisms that underlie it. This observation also draws into question whether EA treatment will be effective for enuretics with any LUTS.

With this question in mind, we designed a study to investigate the therapeutic efficacy of EA treatment for PRNE patients who had been diagnosed as either MNE or NMNE. We previously reported that EA was effective as a second-line therapeutic option for partial or nonresponders to pharmacotherapy.¹⁸ In the present study, we expanded on this subject by including cases with NMNE or relapsed NE. We found that 29 of the 54 partial/nonresponder MNE (53.7%) and 10 of the 25 partial/nonresponder NMNE (40%) patients exhibited FR after EA treatment was instituted, which suggests that adding EA treatment to the original treatment regimen yielded superior results compared with the effect of pharmacotherapy alone. Although the children with PR to pharmacotherapy were more likely to achieve FR after EA treatment than those with NR to pharmacotherapy (Fig. 2), the latter children were significantly more likely to exhibit better response, compared with pharmacotherapy alone, than the former (81.8% vs 54.4%, $P = .024$). Thus, adding EA treatment to the treatment regimen seems to be effective even for children who are completely refractory to primary pharmacotherapy. With respect to bladder capacity, we observed that children with a small bladder capacity tended to achieve FR more frequently than children with normal bladder capacities, although this difference did not achieve statistical significance; this has also been observed previously.² We think that this lack of statistical validity between 2 groups might result from the small size of the study population. Interestingly, of the 28 children with NMNE (including 3 who had relapsed), 11 (39.3%) attained dryness during the daytime. In addition, the majority (8/9) of children with FR to EA treatment combined with pharmacotherapy in group 2 showed continued success. We have assumed that increased bladder reservoir function, namely MVV, by previous anticholinergics seems to improve the continued success rate of EA treatment, al-

though it is deemed controversial in the previous literature.^{19,20} However, from our data, we could not claim sufficient evidence that supports the efficacy of EA treatment for NMNE because our study was not a prospective, randomized study and included a selected population. Moreover, of the 19 children who were younger than 7 years, 7 (38.4%) showed FR and 6 exhibited continued success after the treatment was stopped. Thus, EA treatment even appears to be effective for NE in younger children, as has been reported previously.²¹

One limitation of this study is that it is a retrospective study on selected population with a small sample size. This study included only children with PRNE to assess the therapeutic efficacy of EA combined with primary pharmacotherapy; hence, there was no control group who received EA as monotherapy. Another is that we did not measure the volume of bedwetting to estimate nocturnal bladder capacity; rather, we used the MVVs recorded in a 3-day bladder diary. However, to our knowledge, our study is the first report that shows how EA can complement primary therapies in clinical practice for NE with diverse characteristics. Our study population is different from those of previous studies.¹²⁻¹⁴ Although our findings suggest that adding EA to the pharmacotherapeutic regimen is an effective treatment option for NE that is refractory to the primary therapy, it remains unclear why some NE cases are refractory to primary treatment and which treatment should be instituted. To answer these questions, a prospective study using a larger population is needed.

CONCLUSIONS

In our study, half of the children with PRNE achieved FR after EA treatment combined with pharmacotherapy. Almost two thirds of full responders continued to be dry after withdrawal of treatment. Thus, adding EA treatment to pharmacotherapy is an effective second-line therapeutic strategy for children with PRNE.

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