

Combination of Alarm-intervention and Reboxetine in Therapy-Resistant Enuresis

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Abstract

Introduction: The first-line treatments of primary monosymptomatic night enuresis (PMNE) are alarm intervention and desmopressin. Some patients are resistant to these modes of treatment. Therefore Reboxetine has been used to treat PMNE in these scenarios in recent years and published in many studies. The aim of the study was to determine effectiveness and safety of combination of Alarm intervention and Reboxetine, to treat patients with therapy-resistant enuresis. **Material and Methods:** Two hundred and nineteen children of both sexes were participated in the experiment (average age, 11.3 years). Participants were divided into three groups: Group A (71 patients, Alarm intervention), Group B (79 patients, Reboxetine as monotherapy), Group C (69 patients, Alarm intervention + Reboxetine). The duration of treatment was twelve weeks, followed by follow-up period of twelve weeks to see efficacy. **Result:** There was no significant change in number of enuresis episodes per week before and after treatment in a group B. The number of enuresis episodes per a week (weekly) in a group C reached: before treatment 5.3 (1.5), after treatment 1.0 (0.8), 3 three months after the end of treatment 0.7 (0.7). The percentage of patients with PMNE in a group C was significantly less immediately after the course of treatment (17.4%), and three months after treatment (24.6%). **Conclusion:** Combined treatment of therapy-resistant enuresis with use of Alarm Intervention and Reboxetine gives a high percentage of cured patients both immediately after therapy (82.6%) and three months after the end (75.4%).

Key words: enuresis, alarm intervention, reboxetine

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Introduction

The need for increasing the effectiveness of enuresis therapy remains a topical problem at the present time^{1,2,3}. The prevalence of PMNE is from 1.6%⁴-5.3%⁵ in adolescents, up to 7.5%⁶ 12.4%⁷ among 5-10 year old children. International Children's Continence Society (ICCS) and National Clinical Guideline Centre, UK is recommended the Alarm intervention and desmopressin as a first-line treatment of primary monosymptomatic night enuresis. Both these recommendations have been used for a long time in

therapeutic practice; they have both advantages and disadvantages^{8,9}.

Alarm intervention (AI) isn't associated with exposure to the body's water balance. The duration of AI, in accordance with the recommendations of International Children's Continence Society, is twelve weeks, but can be prolonged until to achieve the therapeutic effect. The positive therapeutic result refers not less than fourteen "dry nights" in a row. This result is achieved among 50-75% of patients, usually after long-term treatment^{10,11,12}. Approximately the same result is achieved with desmopressin, however, after the drug is discontinued, episodes of enuresis are often reappears.

Simultaneous use of AI and administration of desmopressin produces the marked therapeutic effect during the treatment; however, in many patients with desmopressin withdrawal, symptoms of enuresis are rebounded. In addition, combined therapy using AI and desmopressin does not lead to the expected results in 15-25% of patients¹³. Therefore, the search for alternative treatment of primary monosymptomatic night enuresis is continuing. For example, to treat of enuresis, the antimuscarinic drugs (AM) are used¹⁴. It is known that AM by affecting on some receptors, reduce the tone of detrusor and reduce the frequency of urination^{15,16}. To date, it was found that while AM having certain capacity for the primary monosymptomatic night enuresis treatment, their usage doesn't bring to a significant increase in the number of recovered^{17,18,19}.

Another direction to research about effective methods for primary monosymptomatic night enuresis therapy is to use of tricyclic antidepressants (TA) as monotherapy or in combination with other methods. Implementation of TA Imipramine showed that this drug can be very effective to reduce the number of episodes of enuresis. However, Imipramine is potentially cardiotoxic, so it can't be widely used in pediatric practice^{17,20}. An alternative to Imipramine may be another antidepressant drug Reboxetine. Reboxetine selectively inhibits the reuptake of norepinephrine with presynaptic nerve endings, promotes the accumulation of the neurotransmitter in the synaptic cleft and enhances noradrenergic transmission. When taking Reboxetine, there are minimal short-term side effects. Previous studies with Reboxetine shows have encouraging data on the primary monosymptomatic night enuresis as well has minimal short term side effects which doesn't require any treatment^{17, 20,21,22}.

Therefore, the purpose of our work was to research the effectiveness and safety of combination use Alarm intervention and Reboxetine. We also intended to find out how long the positive results of such therapy can be

retained. We suggested that, perhaps, the use of Alarm intervention against the background of psychotropic effects that Reboxetine provides will increase the effectiveness of treatment and the sustainability of results.

Material and Methods

The prospective, randomized trial was conducted at the urological center of Polyclinic No. 3, the diagnostic department of the Children's Medical Association No. 2 of Vladivostok and at the Far Eastern Federal University (Vladivostok) from January 1 till June (December) 30, 2014. The two hundred and nineteen children aged 9-14 (11.3 years old in average) were enrolled in this study; of them, there were one hundred twenty four boys (10.5) and ninety five girls (11.8), who sought medical attention for recurrent PMNE. At least 6 months before the beginning of our experiment, each of the participants had already been treated for the primary monosymptomatic enuresis using AI, desmopressin or a combination of these methods and had not got the expected result. In other words, in children who received treatment earlier, after the previous attempt, the number of episodes with enuresis did not decrease significantly (according to the data of F112u outpatient cards). Thus, those suffered from urination while sleeping and previously unsuccessfully took treatments with Alarm intervention or took desmopressin for at least twelve weeks were the patients enrolled in the study. We verified such cases as "resistant" to the PMNE treatment.

When randomizing patients, the blind random sample method was used. In accordance with the study design (Figure 1), all children were randomly enrolled in three intervention groups: group A (74 seventy one persons, the treatment method was Alarm intervention), group B (79 seventy nine persons, the treatment method was Reboxetine administration), group C (69 sixty nine persons, the treatment method included Alarm intervention + Reboxetine administration). The withdrawal criteria were as follows: the increased level of antidiuretic hormone in the blood (the value less than 1.5 ng/L with an osmolarity level of 270-280 mOsm/L was taken as the norm), helminthes invasion, overactive bladder.

In compliance with the recommendations of ICCS and NCGC (UK), the examination and observation algorithm included the following points. The preliminary stage: the questionnaire survey was carried out using the OAB-q SF questionnaire²³, uroflowmetry²⁴, and laboratory tests (the blood test, urinalysis, the stool analysis). Anthropometric characteristics of patients and the preliminary examination results are presented in Table 1.

The children were treated according to their treatment group for three months followed by observation for another twelve weeks. The observation stage: during the treatment (twelve weeks) and after the treatment discontinuation (twelve weeks): urination diaries were used²⁵ where patients recorded their episodes of urination while sleeping, self-sufficient awakenings when desiring to urinate, dry nights.

As a therapeutic agent, the Wet Stop / BYE-WET signaling system in the standard configuration produced by PALCO LABS, Inc. (USA) was used in the group A. Before the treatment course had begun, patients, their parents or guardians were instructed on the use policies of Alarm systems. In the group B, the Reboxetine administration per 0.4 mg once daily was used as a therapeutic agent. In group C, children applied the Alarm systems, and simultaneously took Reboxetine per 0.4 mg once daily. The written informed consent to participate in the experiment was received from the parents of all patients. The total period of children observation amounted to 6 months.

The JMP SAS Statistical Discovery 8.0.2 (SAS Institute, Cary, NC, USA) software was used for accumulation and statistical processing of information. In order to compare the results, the Wilcoxon test was used, and the correlation of changes in the samples was carried out using the Spearman's rank correlation coefficient. $P < 0.05$ was considered to be sufficient to recognize that differences between characteristic values in groups are significant.

The design of the study was approved by the Ethics Committee of the Far Eastern Federal University on December 17, 2014

Results

All three groups of children (Table 1) who underwent different treatments were homogeneous both for anthropometric measures and for health status. At the start of the study, the number of points accordingly to the OAB-q SF questionnaire scale (2.1 ± 0.4 ; 2.5 ± 0.9 ; 2.6 ± 1.4), parameters of uroflowmetry, the average number of enuresis episodes per week (4.7 ± 0.8 ; 6.1 ± 1.2 ; 5.3 ± 1.5), daytime and nighttime frequencies of urination were not significantly different in patients of all three groups. The average level of antidiuretic hormone was 1.2 (0.7) ng/L (with the osmolarity level of 270-280 mOsm/L), and in each case of the observation, it corresponded to the norm values. The blood tests and urinalyses were appeared to be within norms, the signs of helminthes invasion were not revealed. Thus, the initial parameters with which patients began to receive treatment were identical.

Table 2 shows the number of enuresis episodes before and after three months of the treatment in each of three groups. In patients, who used the Alarm systems, the number of enuresis episodes after the treatment was significantly lower, than before the treatment ($p < 0.05$), but 3 three months later, it increased more than two times. In patients taken Reboxetine, the number of enuresis episodes was statistically homogeneous throughout the whole treatment period and after it had completed. In patients who used the combination therapy, the number of enuresis episodes after the treatment decreased more than times ($p < 0.01$) and did not increase throughout three months after the treatment end ($p < 0.01$). Being registered three months after the treatment, the number of enuresis episodes in these patients significantly differed from their number in children who used the Alarm Intervention as a monotherapy (2.7 (1.1) versus 0.7 (0.7)**), $p < 0.05$). Three months after the completion of the active phase of the study, number of 'dry nights' in patients received the combination therapy was significantly higher than in those received monotherapy (correspondently, $p < 0.01$; $p < 0.05$).

The percentage changes in children with primary monosymptomatic night enuresis during the study are presented in Figure 2. The percentage of children with primary monosymptomatic night enuresis who received Reboxetine had decreased by 16.5% for the whole observation period. The percentage of children with PMNE who used AI had decreased to 40.8% by the end of the active phase of the study. However, three months later, it again increased to 56.3%. The percentage of children with PMNE who received the combination therapy was 17.4% after the treatment and 24.6% three months after the treatment completion. Thus, in the time point of three months after the treatment had ended, the percentage of children with PMNE who underwent the combined therapy was significantly lower than of those received the monotherapy ($p < 0.01$; $p < 0.05$).

The percentage changes of children with PMNE during the study were presented in Figure 2.

The correlation between the curve describing the number of enuresis episodes in children who received the combination treatment with the analogous curve for children who received the Alarm systems only was numerically equal to $r = 0.71$, $p < 0.05$; and with the curve describing data in children who received the Reboxetine therapy only - to $r = 0.49$, $p < 0.05$.

The children who received the monotherapy by Alarm Intervention did not complain about side effects during the treatment. On the contrary, seventeen (11.5%) cases of side effects were recorded in both groups of

children taken Reboxetine (both as the monotherapy and in combination with the Alarm Intervention application, $n = 148$). In teen (6.7%) cases, children complained of short-term dry mouth, in five (3.4%) cases - difficulties when falling asleep, and in two (1.3%) cases - dizziness. All these symptoms were short-term, self-limited reactions and passed in themselves without the drug withdrawal.

In the course of the study, eleven persons (5.0%), seven boys and 4 four girls, refused to participate in it. In six cases (2.7%), the refusals of observation and treatment were associated with acute inflammatory diseases of the upper respiratory tract, and in five cases - with non-treatment reasons.

Table 1: Descriptive characteristics and physiological parameters of children, who took part in study ($n=219$).

Parameters	Group A ($n= 71$)		Group B ($n= 79$)		Group C ($n= 69$)	
	Mean or N	SD or %	Mean or N	SD or %	Mean or N	SD or %
Average Age	10.7	1.5	12.7	2.2	11.4	1.9
Female	28	39.4	34	43.0	33	47.8
Previously used AI	35	49.3	42	53.2	24	34.8
Previously used desmopressin	23	32.4	27	34.2	19	27.5
Previously used AI + desmopressin	13	18.3	10	12.6	26	37.7
Episodes of enuresis/ week	4.7	0,8	6.1	1.2	5.3	1.5
Daytime frequency of urination	6.4	2.6	6.0	2.1	6.3	1.5
Nighttime frequency ¹ of urination	1.7	0.5	2.4	0.9	1.4	1.2
Qaver, ml/sec	10.4	3.6	9.1	2.5	12.3	3.8
Qmax, ml/sec	13.2	4.5	13.0	3.1	15.5	4.3
Volume of bladder, ml	104	26.7	97	37.6	94	28.7
OAB-q SF, score	2.1	0.4	2.5	0.9	2.6	1.4

Remark SD – standard deviation.

¹ Including episodes of enuresis

Table 2: Changing the number of episodes enuresis and "dry" nights before, after and 3 three month after treatment in groups A (Alarm intervention, $n=71$), B (Reboxetine 0.4 mg per oral /day, $n=79$) and C (Alarm Intervention+Reboxetine 0.4 mg per oral/day, $n=69$)

Period of observation	The average number of episodes of enuresis (per week)			The average number of "dry" nights (per week)		
	Prior to treatment	At once after treatment	Three month after treatment	Prior to treatment	At once after treatment	Three month after treatment
Group A	4.7 (0.8)	1.2 (0.9)*	2.7 (1.1)*	2.9 (0.8)	5.7 (1.0) *	4.3 (1.3)
Group B	6.1 (1.2)	5.3 (2.0)	5.6 (0.9)	1.2 (1.2)	1.9 (1.6)	2.0 (1.4)
Group C	5.3 (1.5)	1.0 (0.8)**	0.7 (0.7)**	1.9 (0.9)	6.1 (1.3)**	6.3 (1.1)**

Remarks: In parentheses is the standard deviation (SD). The significance of differences * $p < 0.05$; ** $p < 0.01$. In the second column of the table compares the number of episodes of enuresis at the beginning of the study, immediately after treatment and three months after treatment. This also applies to the comparison of the average indicators of «dry» nights. Mean number of enuresis episodes per week may be greater than the average number of «wet» nights (seven minus the number of «dry» nights), as some children had two and three episodes of enuresis per night.

Discussion

There are many literature data on both the advantages and disadvantages of Alarm Intervention as an effective treatment for primary monosymptomatic night enuresis. The disadvantages of AI include, first of all, the lack of stability of the results obtained ^{8,10,11,12,26,27}.

Simultaneously with the use of methods recommended by ICCS, it searching for treatment methods and drugs which can increase the effectiveness of treatment. In the urological literature of the last decade, the successful experience with the use of Reboxetine for the treatment of primary monosymptomatic night enuresis has been repeatedly reported, especially in

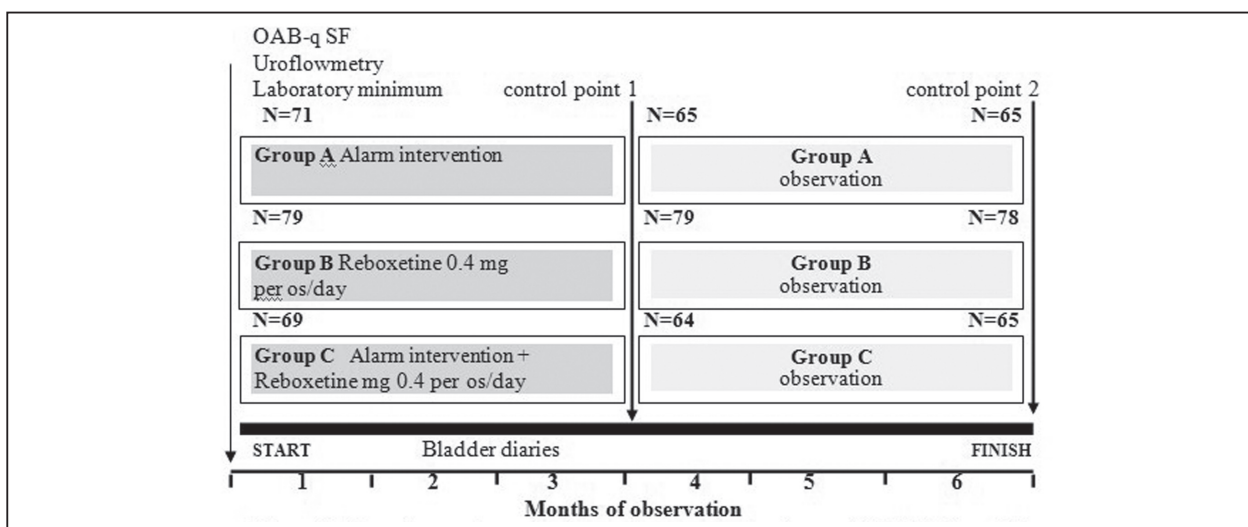


Fig 1: The scheme of examination and treatment of patients with PMNE (n=219)

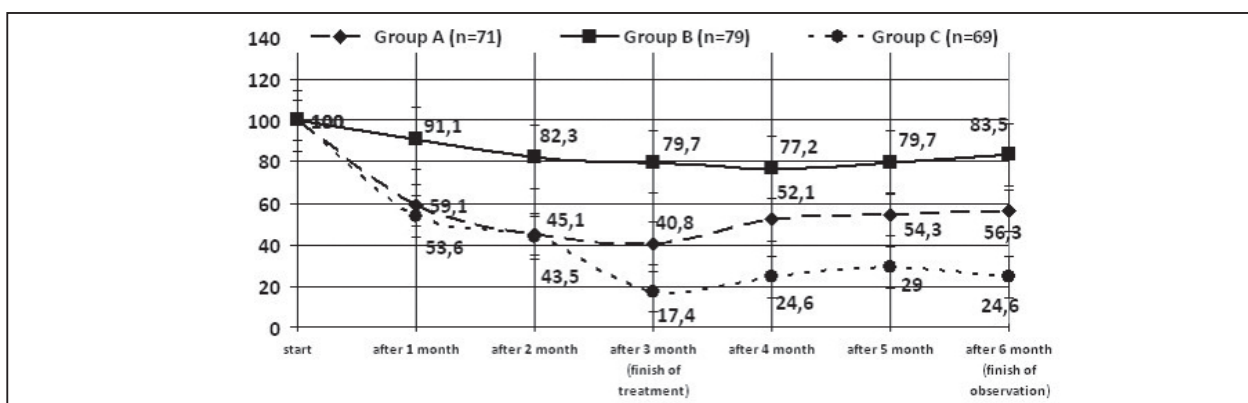


Fig 2: The change of the percentage of patients with PMNE.

Group A Alarm intervention; **Group B** Reboxetine 0.4 per os/day; **Group C** Alarm intervention + Reboxetine 0.4 per os/day

patients with unsuccessful experience with traditional treatments^{20,21,22}. Thus, in this study, we tried to find out the effectiveness of AI supplemented with Reboxetine in cases of resistance to ICCS recommended treatments.

Our study showed that Reboxetine reception as the only means of treatment of treating therapy-resistant enuresis provides no more than 16.5% of the cure. The result of using AI as a monotherapy is consistent with the literature data about insufficient effectiveness of this method (in our case, 60%), and about instability resulting effect. After 3 months after the end of treatment, only 43.7% of patients did not have of PMNE symptoms.

We found that the combination of AI + Reboxetine is significantly more effective than monotherapy (both immediately after treatment and at 3 three months after the end). That result might be associated with the specific effects of AI on children taking Reboxetine.

It is known that Reboxetine highly selectively inhibits the reuptake of norepinephrine by presynaptic nerve endings, promotes accumulation of the neurotransmitter

in the synaptic cleft, and enhances of noradrenergic transmission^{28, 29}. A high level of norepinephrine in the presynaptic nerve endings affecting on the work of the limbic-reticular formation, changes the structure of sleep.

Perhaps increase the duration of REM sleep improves perception of Alarm signal and enhances the effect of AI.

In addition, as an antidepressant, Reboxetine has a specific effect on the child: it reduces emotional tension and anxiety, increases mental activity, which perhaps, in some cases, avoids a negative reaction to wet bed. These effects allow the more rationally applying of AI.

Of course, our work is not yet done. It seems interesting to further study about therapeutic action of Reboxetine and AI in a wide range of time and test a hypothesis that Reboxetine improves long-term results of treatment using AI. Also, it would be interesting to study the combined effects of Reboxetine и Desmopressin.

Conclusion

The combined effects of Alarm Intervention and Reboxetine were effective in therapy-resistant enuresis. Combination therapy, in contrast to treatment with only

Alarm Intervention, leads to a more sustainable result, which persists for at least three months after the abolition of therapy. When taking Reboxetine, short-term, minor and spontaneously disappearing side effects are noted.

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