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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

The Efficacy of Combination Therapy for Treating Enuresis Nocturna

Enürezis Nokturna Tedavisinde Kombinasyon Tedavisinin Etkinliği

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Abstract

Objective: Monosymptomatic enuresis nocturna treatment at pharmacological and non-pharmacological treatments are used in In our study, we aimed to compare the long-term results of desmopressin (DP) treatment and combined DP-enuresis alarm device (DP/EA) treatment.

Methods: A total of 39 patients with the diagnosis of monosymptomatic enuresis nocturna, 25 using DP treatments and 14 using DP/EA treatments, were included in the study. Long-term data of the patients were obtained and compared retrospectively.

Results: While there was no significant difference in terms of recurrence in both groups after the treatment, it was observed that the duration of drug use and the dose of drug used by the patients in the combined treatment group were similar. It was observed that duration at drug used for 8.80±6.12 months (n=25, p=0.0025) in the DP group and 5.71±1.33 months (n=14, p=0.025) in the DP/EA group. It was observed that the total drug dose used in the DP group was 880.8±520.09 micrograms (n=14, p=0.022) and 542.14±194.94 micrograms (n=14, p=0.022) in the DP/EA group. In long-term follow-ups, recurrence was observed in 28% (n=25, p=0.445) patients using DP and 18% (n=14, p=0.445) patients using DP/EA.

Conclusion: When DP and DP/EA treatment are compared, it is observed that there is no difference when long-term recurrence is considered. However, it is observed that DP/EA combined treatment shortens the duration of treatment and reduces the dose of drugs used during treatment.

Keywords: Enuresis nocturna, desmopressin, combined therapy

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Öz

Amaç: Monosemptomatik enürezis nocturna tedavisi farmakolojik ve non-farmakolojik olarak ikiye ayrılmıştır. Çalışmamızda desmopressin (DP) tedavisi ile kombine DP enürezis-alarm cihazı (DP/AC) tedavisinin uzun dönem sonuçlarını karşılaştırmayı amaçladık.

Yöntem: Monosemptomatik enürezis nokturna tanılı 25 DP tedavisi alan ve 14 DP/AC tedavisi alan toplam 39 hasta çalışmaya dahil edildi. Hastaların uzun dönem verileri retrospektif olarak değerlendirildi ve karşılaştırıldı.

Bulgular: Tedavi sonrası her iki grupta nüks açısından anlamlı fark bulunmazken, kombine tedavi grubundaki hastaların ilaç kullanım sürelerinin ve kullandıkları ilaç dozunun az olduğu görüldü. İlaç kullanma süresinin DP grubunda 8,80±6,12 ay (n=25, p=0,0025), DP/AC grubunda 5,71±1,33 ay (n=14, p=0,025) olduğu görüldü. DP grubunda kullanılan toplam ilaç dozunun 880,8±520,09 mikrogram (n=14, p=0,022) ve DP/AC grubunda 542,14±194,94 mikrogram (n=14, p=0,022) olduğu görüldü. Uzun dönem takiplerde DP kullanan hastalarda %28 (n=25, p=0,445) ve DP/AC kullanan hastalarda %18 (n=14, p=0,445) nüks görüldü.

Sonuç: DP ve DP/AC tedavisi karşılaştırıldığında uzun süreli nüks düşünüldüğünde fark olmadığı görülmektedir. Ancak DP/AC kombine tedavisinin tedavi süresini kısalttığı ve tedavi sırasında kullanılan ilaç dozunu azalttığı görülmektedir.

Anahtar Kelimeler: Enürezis nocturna, desmopressin, kombine tedavi

Introduction

Monosymptomatic enuresis nocturna (MNE) is defined by the International Child Continence Society (ICCS) as intermittent incontinence only during sleep in children older than 5 years of age, without associated lower urinary tract and bladder dysfunction[1]. The overall prevalence is around 15% at the age of 5 years[2]. About 15% of cases heal spontaneously within year[3]. The disease is tried to be explained by three pathological mechanisms. The first is polyuria occurring during sleep, the second is bladder dysfunction occurring during sleep, and the third is waking disorder[4,5]. The most commonly used methods in treatment are supportive therapy, alarm therapy, and drug therapy[6,7]. In our study, we aimed to compare the results of patients who used oral desmopressin (ODP) alone in MNE patients with those who used ODP combined with enuresis alarm therapy (ODP/EA).

Materials and Methods

Study was approved by University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Local Ethics Committee (decision no: 2023/04-43, date: 03.05.2023).

The data of 96 patients diagnosed with MNE in our clinic between 2010 and 2020 were retrospectively evaluated. The data of 25 patients who used DP and 14 patients who received DP/EA combination therapy who met the study criteria were included in the study. Patients aged 5-16 years who met the (ICCS) criteria, had urinary incontinence more than 2 times a week at night, had no urological and neurologic disease, had regular follow-up visits, discontinued their medical treatment, and were followed for at least 12 weeks thereafter were included. Patients with another urological, neurological, cardiovascular system disease who were on any medication, had irregular follow-ups, had abnormal urine results, interrupted or terminated treatment for any reason, and had previously received unsuccessful enuresis treatment were excluded from the study. Detailed histories were taken, and physical examinations of the patients were performed at the outpatient clinic application. Patients with a preliminary diagnosis of MNE according to the ICCS definition were evaluated with urinalysis and biochemical tests. Fluid restriction was started 2 h before bedtime in patients diagnosed with MNE. Patients who were allowed to go to the toilet while lying down were allowed to lie down with an empty bladder. Patients receiving ODP treatment were allowed to absorb 120 micrograms of oral desmopressing without water under their tongue while lying down. The dose was increased up to 240 mgr in patients who did not respond to treatment (1 wet night/week) among the patients who were called for control after 2 weeks. After the response to the treatment, the patients were called for control at 4-week intervals. Patients who responded to the treatment were treated with ODP at a dose that kept them dry for 3 months. After 3 months, half of the dose he used was reduced and ODP was continued at this dose for another month. Patients who relapsed (1 wet night/week) were increased to the previous dose and dose reduction was attempted 1 month later. In patients who remained dry, treatment was applied for 1 more month by reducing half of the last dose used. In patients who used 60 mgr ODP for 1 month and remained dry, 30 mgr ODP was used once a day for 1 more month and drug treatment was terminated.

While oral desmopressing treatment was applied as in the first group in patients receiving ODP/EA treatment,

an EA device was used every night while lying down with ODP during the period when the drug treatment dose was reduced after only 3 months of dryness. After the patients' response to treatment, controls were performed at 4-week intervals similar to the patients in the ODP group. After ODP treatment was discontinued, EA treatment was used for another 3 months. All patients were followed up after the treatment was stopped by calling them for controls every 2 months.

Statistical Analysis

Analysis was performed with the SPSS 23 (SPSS Inc., Chicago, IL, USA) packaged program statistical analyzes were performed using paired or independent t-tests when appropriate for continuous variables and chi-square tests for categorical variables. The treatment outcomes (response, non-compliance, and relapse rates) were compared using chi-square tests. Differences in the mean number of wetting episodes per week before treatment, at the end of treatment, and at the end of follow-up were assessed using one-way analysis of variance (ANOVA). Within-group comparisons over these 3 time points were performed by paired t-test. significance, $p<0.05$ was considered significant at the 95% confidence interval.

Results

The distribution of general information of 34 patients is given in Table 1. A total of 39 patients were included in the study, and 25 of them were treated with DP alone, while 14 were treated with DP/EA. The mean age of the patients was 9.73 years, and the follow-up period was 21 months after treatment. The information about the patients after separation according to the treatment protocols are given in Table 2 and Table 3. It was observed that there was no difference between the treatment groups in terms of gender, constipation, age, and follow-up period. However, when the dose used was compared, it was observed that the total dose used in the DP group was 26928.00±18871.26 micrograms, in the DP/EA group it was 16200.00±5980.35 micrograms and was significantly higher in the DP group (p=0.015). When the duration of drug treatment was examined, it was observed that it was 9.24±6.05 months in the DP group, 5.86±1.65 months in the DP/EA group, and that it was significantly longer in the DP group (p=0.013). However, when the relapse rates after treatment were examined, it was observed that the recurrence rate was 28% in the DP group, 18% in the patients using DP/EA, and there was no significant difference between the two groups (p=0.445).

Table 1. Demographic data of the patients

Gender (famele/male)	15 (38.5)/24 (61.5)
Constipation (no/yes)	35 (89.7)/4 (10.3)
Alarm device (no/yes)	25 (64.1)/14 (35.9)
Relapse (no/yes)	30 (76.9)/9 (23.1)
Age (year)	9.73±2.26
The drug dose (total dose)	759.23±531.92
Treatment duration (months)	7.69±5.15
Follow-up time (months)	21.32±11.08

Table 2. Characteristics of the patients by groups

		DP (n=25)	DP + EA (n=14)	p
Gender	Female	11 (44)	4 (28.6)	0.342
	Male	14 (56)	10 (71.4)	
Constipation	No	22 (88)	13 (92.9)	0.999
	Yes	3 (12)	1 (7.1)	
Relapce	No	18 (72)	12 (85.7)	0.445
	Yes	7 (28)	2 (14.3)	

DP: Desmopressin, EA: Enuresis alarm

Table 3. Results of the patients by groups

	DP (n=25)	DP + EA (n=14)	p
Age (year)	9.04±2.54	11.00±3.47	0.051
Dose (total dose/mcg)	26928.00±18871.26	16200.00±5980.35	0.015
The duration of treatment	9.24±6.05	5.86±1.65	0.013
The duration of follow-up after treatment (monht)	20.17±11.44	23.46±10.49	0.369

DP: Desmopressin, EA: Enuresis alarm

Discussion

Both pharmacological and non-pharmacological treatments are used in the treatment of MNE. Although the success rate of treatment has increased as the pathophysiology of the disease has become clear in recent years, treatment is not possible in all patients[8-10].

High cost and high recurrence rate are the most important problems in desmopress, which is the most frequently used and usually the first treatment option. The most important side effect is hyponatremia, and it is generally observed in patients who do not regulate their water intake[11]. Other pharmacological agents, tricyclic antidepressants and anticholinergics are used in the treatment of MNE. Although imipramine is a frequently used tricyclic antidepressant, its use has decreased in recent years due to its high side effects and recurrence rates[12]. The anticholinergic agent oxybutynin is preferred especially in patients with low bladder capacity[13].

Alarm therapy, which is the most commonly used non-pharmacological treatment, is more successful in terms of side effects and recurrence rates. However, the late onset of its effect reduces the treatment motivation of the family and the child. Technical difficulties and difficulty in use are other important disadvantages[14,15].

Supportive treatments such as regulation of fluid intake, keeping a voiding diary, regulation of toilet training, awakening from sleep, and regulation of diet are not used alone due to their low success. In the study conducted by Hussain Shah et al.[16] with supportive treatments, it was reported that only 2% of 10% of patients who responded to treatment remained permanently dry in the long-term. For this reason, it is often used in combination with other treatment options. Despite the treatment options, incomplete results and recurrence in some patients caused both treatments to be applied in different modifications or in combination. DP with oxybutynin and impramine with alarm were used along with DP with alarm. However, it has been observed that the preferred combination in scientific studies is DP with alarm[17-20]. In Bradbury's[21] study, DP/EA combined treatment was compared only with the alarm group, and it was stated that the combined treatment was effective in terms of effect, but there was no difference in terms of recurrence, and combined treatment was recommended in severe enuretic cases. Again, Ahmed et al.[6] In their study comparing EA, DP, and DP/EA groups in Saudi children, it was reported that while better results were observed in patients using DP in the early response, recurrence was higher, long-term response was good, and recurrence was low in the alarm group, while combined treatment was not advantageous in terms of recurrence.

Since we compared two treatments that started with DP treatment in our study, we were not evaluate the early response from the treatments of the patients. We only wanted to compare the long-term advantages and outcomes of the DP group with complete response to treatment and the DP/EA group. In our study, it was observed that the treatment of children using DP lasted longer and they needed to use more drugs. However, it was observed that there was no difference between the two groups in terms of recurrence in the long-term. In our study, adding EA treatment to DP treatment provided a quick response to treatment, patient compliance was higher and treatment duration was longer. We watch it shorten. In addition, it is observed that the use of lesser doses of drugs in short-term treatment reduces the cost of treatment. The most important deficiencies in our study were the absence of a control group and a group of patients treated only with EA. We know that MNE is a disease that tends to resolve spontaneously, and EA treatment is still a very active treatment method today. Since we started the treatment of all patients with DP in our study, we thought that it would be meaningless to evaluate the response to treatment, and we examined how adding EA to treatment would make a difference in the long-term treatment in patients using DP who responded to treatment.

As a result, when the DP and DP/EA groups, which are one of the treatment methods used in the treatment of MNE, were difference was observed in terms of recurrence in the long-term results of patients using DP and patients using DP/EA together. However, in patients using DP/EA, drug treatments were discontinued in a shorter time and fewer doses of drugs were used. The combined use of DP/EA, due to shorter drug use, reduced the patient's treatment cost.

Study Limitations

The main limitation of the study was its retrospective design. The study had a limited number of patients. Therefore, more extensive and multicenter studies are needed. Long-term follow-ups are needed for a healthier evaluation of the study results.

Conclusion

Treatment of enuresis nocturna is a disease that appears common in pre-adolescent childhood and resolves almost

90% by the age of 18. The pharmacological treatment of enuresis nocturna pays a price to the national economy. In this study, we have shown that the cost of combination therapy and the dose of drugs used can be reduced.

Ethics

Ethics Committee Approval: Study was approved by University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Local Ethics Committee (decision no: 2023/04-43, date: 03.05.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.Ş., M.Y., E.K., Concept: U.Ş., B.E., O.D., Design: H.Ü., E.K.A., M.Z.K., Data Collection or Processing: M.Y., T.K.Y., M.Z.K., Analysis or Interpretation: U.Ş., M.Y., Literature Search: U.Ş., M.Y., E.K., H.Ü., M.Z.K., Writing: U.Ş., M.Y., T.K.Y., H.Ü., E.K.A., M.Z.K.

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