Better outcomes with desmopressin melt than enuretic alarm therapy in children with nocturnal enuresis during coronavirus disease 2019 (COVID-19)

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Abstract

Objectives: This study aimed to investigate the effect of the coronavirus disease 2019 (COVID-19) pandemic on the treatment of children with primary monosymptomatic nocturnal enuresis (MNE) with desmopressin melt versus an enuresis alarm.

Materials and methods: This study included 56 children with primary MNE who were taking desmopressin melt or using an alarm. Their anxiety levels were evaluated using the Social Anxiety Scale for Children-Revised. For both treatment methods, data from a 3-month bedwetting diary between the third and sixth months of the pre-pandemic treatment were compared with those assessed during the same period during the pandemic.

Results: Prior to the COVID-19 pandemic, the median 3-month mean frequency of MNE was 1 (0–7.67) in children using desmopressin melt versus 1.33 (0–6) in those using alarm treatment ($p = 0.095$). During the COVID-19 pandemic period, the median monthly mean frequency of MNE was 1.33 (0–7.33) in children using desmopressin melt versus 6 (1.33–13) in those using alarm treatment ($p < 0.001$).

Conclusions: The COVID-19 pandemic and its accompanying psychological effects did not affect the treatment efficacy of desmopressin melt in children with primary MNE but did adversely affect that of enuresis alarms.

Keywords: COVID-19; Desmopressin melt; Enuresis alarm; Nocturnal enuresis

1. Introduction

Nocturnal enuresis (NE) is one of the most common reasons children present to outpatient urology clinics. NE negatively affects children and their parents psychologically, emotionally, and socially. Although environmental, genetic, and psychological factors reportedly play a role in NE, its etiopathogenesis remains unclear.[1] In more than 60% of children, NE is not accompanied by lower urinary tract symptoms and bladder or bowel dysfunction; thus, it is referred to as monosymptomatic NE (MNE). It is classified as primary or secondary depending on whether it has continued uninterruptedly since birth or had ever resolved for at least 6 months.[2] Different treatment options, including behavioral therapy, pharmacotherapy, enuresis alarms, and their combinations, are used in children with primary MNE. The most common options, that is, enuresis alarms and desmopressin treatment, have proven effective in many studies.[3]

Coronavirus disease 2019 (COVID-19) was first identified in China in December 2019 and declared a global pandemic by the World Health Organization in March 2020.[4] The first detected case of COVID-19 in Turkey was announced by the Ministry of Health on March 11, 2020, while the first related death occurred on March 15, 2020.[5] With the first death seen and the spread of the pandemic throughout the country over time, government officials took some precautions. The use of masks has become a part of our daily lives. Curfews began for all citizens except those declared essential. Schools were suspended indefinitely. Death became a frequent topic of discussion, which created fear. The media began talking about the daily number of deaths and cases. All people became directly or indirectly affected by the situation.

The likelihood of children being infected by its causative virus, sudden acute respiratory syndrome coronavirus 2, is lower than that of the adults. If the infection occurred in children, it was asymptomatic or involved only mild symptoms. Nevertheless, this does not mean that children are affected less by the pandemic than adults; rather, many children either lost relatives to COVID-19 or heard about the numerous deaths. With the closure of schools and the implementation of isolation, children moved away from their social environments and were restricted to their homes. Owing to the continuing pandemic, schools started offering online education. Accordingly, children began to spend more time on tablets and computers. Conditions indirectly created by the pandemic cause anxiety, depression, mood

changes, or sleep disorders in children.[6–8] However, to the best of our knowledge, no such study has been conducted before. Here, we hypothesized that the pandemic would affect this patient group, as children with primary MNE have higher anxiety levels.[9–12] Therefore, the present study aimed to compare the treatment efficacy of desmopressin melt and enuresis alarms in addition to behavioral treatment before and during the pandemic in primary MNE children whose treatment began before the start of the COVID-19 pandemic.

2. Materials and methods

The records of 96 children aged 6–14 years who presented to the urology and pediatrics outpatient clinic of Adana City Training and Research Hospital with NE between June and October 2018 were retrospectively reviewed. The ethics committee approved the study's design. Each child initially underwent a detailed physical examination and urinalysis. Data on the children's urination and defecation habits and daytime lower urinary system symptoms were gathered from the children and their parents. Day and night fluid intake and urination habits were recorded using a 3-day bladder diary. Two weeks of nocturnal urine production was calculated by weighing the night diapers and summing the volume of urine that was first voided in the morning. The expected bladder capacity for the child's age was calculated using the following formula: ([age in years] $\times 30 \pm 30$ mL).[13] Children suspected of having respiratory tract pathologies that might have caused sleep disturbances were referred to an otolaryngologist. Children with high nighttime urine production; overactive bladder; daytime lower urinary tract symptoms; neurological, metabolic, or psychiatric disorders; and who could not comply with treatment were excluded from the study. The study included children who failed to wake in response to a full bladder.[14]

A total of 79 children with primary MNE who received desmopressin melt 120 mg once a day (Minirin melt; Ferring Pharmaceuticals) or an enuresis alarm (Enurin; Aymed Medical Inc.) in addition to behavioral therapy were included in the study. The parents of these children were interviewed by phone and provided with information about the study. The parents of 10 patients refused to participate in the study, while those of 13 others stated that the treatment was discontinued. The study was initiated by making an appointment with the parents of the remaining 56 children. Information was collected personally.

The stress status of children during the pandemic was evaluated using the Social Anxiety Scale for Children-Revised (SASC-R) by providing an environment in which children and parents could feel comfortable. The SASC-R is a self-report scale that was developed by La Greca et al. in 1988.[15] This scale, which consists of 10 items, was revised in 1993 to contain 18 items and 5 options.[16] The scores obtained from the scale were 18 to 90. Simultaneously, the children were questioned and their symptoms recorded using a 3-month bedwetting diary when they were under treatment during the pandemic period.

In our study, the data in the 3-month bedwetting diaries of the treated patients between the third and sixth months of pre-pandemic treatment were compared with those assessed during the first wave of the pandemic (May–July 2019). Thus, we evaluated the effect of the COVID-19 pandemic on primary MNE patients using desmopressin melt or an enuresis alarm in addition to behavioral therapy.

Data are expressed as *n* (%), mean ± standard deviation, or median (minimum–maximum) as appropriate. Normality was

checked using the Shapiro–Wilk test. The Mann–Whitney *U* test or Student's *t*-test was used to examine continuous variables, while Pearson's chi-squared analysis was used to examine categorical variables. SPSS Statistics for Windows version 22.0 (IBM Corp, Armonk, NY) was used for the statistical analysis. Differences were considered statistically significant at $p < 0.05$.

3. Results

A total of 56 children were included in the study. Of them, 31 (55.3%) used desmopressin melt and 25 (44.7%) used an enuresis alarm. There were 19 (61%) male and 12 (38%) female children in the desmopressin melt group, and 16 (64%) male and 9 (36%) female children in the enuresis alarm group. The mean age of the children using desmopressin melt was 9.06 ± 2.502 years, whereas that of those using the enuresis alarm was 9.04 ± 2.245 years ($p = 0.970$). The mean monthly NE value of children taking desmopressin melt was 13.5 ± 2.9 days, while that of the patients receiving alarm treatment was 14.04 ± 3.1 days ($p = 0.550$). Prior to the COVID-19 pandemic, the mean SASC-R score was 23.5 ± 7.8 points in the desmopressin melt group and 24.8 ± 7.8 points in the enuresis alarm group ($p = 0.523$). Independent of treatment method, the mean monthly NE frequency was 1.6 ± 1.6 days prior to the COVID-19 pandemic versus 3.6 ± 3.3 days during the COVID-19 pandemic period ($p < 0.001$). During the COVID-19 pandemic, the mean SASC-R score was 29.19 ± 10.0 points in the desmopressin melt group and 30.32 ± 10.4 points in the enuresis alarm group ($p = 0.684$). The mean SASC-R score of all children prior to the COVID-19 pandemic period was 24.1 ± 7.8, while that during the COVID-19 pandemic period was 29.7 ± 10.1 ($p < 0.0001$). The group distribution, demographics, and clinical characteristics of the children are shown in Table 1.

Prior to the COVID-19 pandemic, the median 3-month mean frequency of NE was 1 (range: 0–7.67) day in children using desmopressin melt versus 1.33 (0–6) days in children who received alarm treatment ($p = 0.095$). During the COVID-19 pandemic period, the median monthly mean frequency of NE was 1.33 (range: 0–7.33) days in children using desmopressin melt versus 6 (range: 1.33–13) days in the alarm treatment group ($p < 0.001$). The frequency of NE before versus during the COVID-19 pandemic period is shown in Figure 1.

4. Discussion

NE has a multifactorial etiology; to date, it includes genetic transmission, disruption of day and night rhythm in terms of antidiuretic hormone secretion, abnormalities in the Barrington core network connecting the brain and bladder, decreased functional bladder capacity, and detrusor overactivity.[17–19] Relatively few studies have investigated the likelihood of associated environmental and psychological factors. Although NE does not involve comorbid psychiatric disorders, the prevalence of generalized anxiety disorder and psychiatric symptoms is higher in affected children than in those without NE.[9–12,20]

Desmopressin is the most common pharmacological agent used to treat NE. The melt formulation, which has been used since 2005, has increased efficacy compared to its previous forms, maintains a more stable plasma concentration, and features a low side effect profile.[21,22] Another common treatment method is enuresis alarms. Linen et al. compared enuresis alarms and desmopressin melt and reported similar
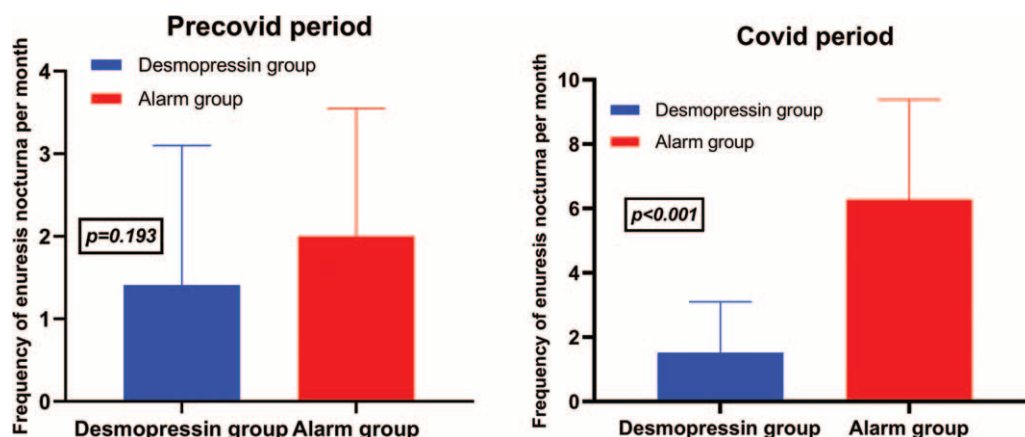
Figure 1. A comparison of the frequency of nocturnal enuresis before and during the COVID-19 pandemic period.

efficacies (68.2% vs. 68.4%). The same study suggested that a 12-week treatment period was required for parents and children to adapt to the alarm treatment and reach maximum treatment efficiency; any evaluation performed prior to that point would be misleading.[2] Although the rate of treatment discontinuation was higher in those using enuresis alarms, post-treatment relapse was more common in those using desmopressin melt.[23–25]

The COVID-19 pandemic has affected many people worldwide. The follow-up of many chronic patients was disrupted owing to the increased patient load in hospitals and, conversely, patient hesitation to present to a hospital. In addition to the abovementioned factors, quarantine, school closures, curfews, travel restrictions, and isolation also played a major role in its effect. Deaths due to COVID-19 have many effects, such as inciting a fear of death in children as well as adults, and predispose children to develop behavioral problems. State-specific behavioral and emotional problems such as anxiety, sleep disorders, and sadness have been observed in children. Many diseases associated with anxiety disorders, including NE, are likely affected by the pandemic.[8] Here we presented the effect of the COVID-19 pandemic on primary MNE children using desmopressin melt and enuresis alarms in addition to behavioral therapy.

Here, we used the bedwetting diary recorded between the 12th and 24th weeks as a scale as suggested by Keten et al. before the pandemic.[2] We used the data obtained from the bedwetting diary at the same period in both groups to ensure intergroup homogeneity. Thus, we compared the time points at which the two treatments would show their maximum effectiveness. In the pre-pandemic period, no difference was noted between enuresis alarms and desmopressin melt, in addition to behavioral treatment, in mean monthly bedwetting episodes. During the pandemic, we observed that patients using enuresis alarm devices had worsened bedwetting diaries than those in the desmopressin melt group. No difference in episodes was noted in the desmopressin melt group before versus during the pandemic. A comparison of follow-up periods indicated no intergroup differences.

Desmopressin melt and enuresis alarms are two methods with different mechanisms. Desmopressin melt, an antidiuretic hormone analog, increases water absorption in the distal tubule, thereby decreasing urine output, whereas the enuresis alarm works through conditional reflex mechanisms.[21,26] We used SASC-R to evaluate the patient anxiety levels in the two groups prior to and during the pandemic. There was no intergroup difference in SASC-R values before versus during the pandemic. The SASC-R values of all children increased during the COVID-19 pandemic. Considering that both groups were exposed to an equal anxiety load, the enuresis alarm treatment efficacy was affected more than the desmopressin melt treatment efficiency.

The limitations of our study include its small number of patients in each group and the absence of a control group that would allow a comparison with pediatric patients without enuresis. However, to the best of our knowledge, this is the first study of its kind in this field.

Table 1

Patient group distributions, demographic variables, and clinical characteristics.

Characteristics	Desmopressin melt group (n = 31)	Enuresis alarm group (n = 25)	p
Age, yr	9.06 ± 2.5	9.04 ± 2.2	0.970[T]
Sex, male/female	19/12	16/9	0.835[*]
Follow-up time, mo	11.06 ± 0.9	11.24 ± 1.0	0.533[T]
SASC-R point	29.19 ± 10.0	30.32 ± 10.4	0.684[T]
Number of enuresis nocturna episodes per month before the COVID-19 pandemic, median (range)	1 (0–7.67)	1.33 (0–6)	0.095[¥]
Number of enuresis nocturna episodes per month during the COVID-19 pandemic period, median (range)	1.33 (0–7.33)	6 (1.33–13)	<0.001[¥]

COVID-19 = coronavirus disease 2019; SASC-R = Social Anxiety Scale for Children-Revised. The special letter symbols indicate the statistical methods performed. The methods are explained in the article.

5. Conclusions

Our study results suggest that, although the COVID-19 pandemic and its accompanying psychological effects on children did not affect the efficacy of desmopressin melt in children with primary MNE, it did affect the efficacy of enuresis alarms. In such cases, a change in treatment or combination therapy may be recommended.

Acknowledgments

Statement of ethics

This study was approved by University of Health Sciences, Adana City Teaching and Research Hospital local ethics committee (30.12.2020-73/1209). Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest statement

The authors report no conflicts of interest.

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Author contributions

EV: Analysis and interpretation of data;
HE: Final approval of the version to be published;
HE, AA and UU: Critically review;
UU and HA: Conception and design;
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