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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Intermittent Prophylactic Rectal Diazepam Treatment in Children with Febrile Seizure

Febril Konvülziyon ile Takipli Çocuklarda Aralıklı Profilaktik Rektal Diazepam Tedavisi

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Abstract

Objectives: Febrile seizure (FS) is the most common neurological disorder in childhood. Intermittent rectal diazepam (DZP) prophylaxis seems to prevent recurrence, however, there remains ongoing discussion regarding its ability to prevent epilepsy. This study aimed to analyze the outcome of intermittent prophylactic rectal DZP treatment on both recurrence and subsequent epilepsy.

Materials and Methods: A total of 229 children with FS and given intermittent rectal DZP prophylaxis between 1 January 2005 and 1 December 2013 were included. Data regarding demographics, clinical characteristics, recurrence of FS, and subsequent epilepsy after intermittent rectal DZP prophylaxis were retrospectively analyzed.

Results: Of 229 patients, 57 (24.9%) patients experienced one or more recurrence. Girls had a higher recurrence rate (36.4% vs. 17.7%) (p=0.002). Patients with complex seizures had a higher recurrence rate (38.6% vs. 20.3%) (p=0.006). Epilepsy occurred in 11.4% of patients. Patients with complex seizures had a higher rate of epilepsy (22.8% vs. 7.6%) (p=0.002). Epilepsy did not occur in patients without recurrence, while the rate of epilepsy is 4.8% in patients with one recurrence, 42.1% in those with two recurrences, and 100% in those with three or more recurrences (p<0.001). The rate of epilepsy increased as the number of recurrences increased after prophylactic rectal DZP treatment.

Conclusion: It is a remarkable finding that as the number of recurrences decreased, the rate of epilepsy also decreased, and none of the patients without recurrence experienced epilepsy. Hovewer, large-scale prospective studies are needed to make a conclusion about the preventing effect of DZP prophlaxis on subsequent epilepsy.

Key Words: Febrile Seizure, Epilepsy, Intermittent Rectal Diazepam, Prophylaxis, Children

Öz

Amaç: Febril konvülziyon (FK) çocukluk çağında en sık görülen nörolojik bozukluktur. Aralıklı rektal diazepam (DZP) profilaksisi rekürrensi önlediğine dair çalışmalar mevcut olup epilepsi gelişmini önlemesi konusunda tartışmalar devam etmektedir. Bu çalışmada aralıklı profilaktik rektal DZP tedavisinin rekürrens ve epilepsi gelişimi üzerindeki sonuçlarını analiz etmek amaçlanmıştır.

Gereç ve Yöntem: 1 Ocak 2005 ile 1 Aralık 2013 tarihleri arasında aralıklı rektal DZP profilaksisi uygulanan FK'li toplam 229 çocuk çalışmaya dahil edildi. Hastaların demografik özellikleri, klinik özellikleri, aralıklı rektal DZP profilaksisi sonrası rekürrens ve epilepsi gelişimi ile ilgili veriler retrospektif olarak analiz edildi.

Bulgular: İki yüz yirmi dokuz hastanın 57'sinde (%24,9) bir veya daha fazla rekürrens görüldü. Kızlarda rekürrens oranı erkeklerden daha yüksekti (%36,4 vs. %17,7) (p=0,002). Komplike nöbetleri olan hastalarda rekürrens oranı daha yüksekti (%38,6 vs. %20,3) (p=0,006). Hastaların %11,4'ünde epilepsi geliştiği görüldü. Komplike nöbetleri olan hastalarda epilepsi oranı daha yüksekti (%22,8 vs. %7,6) (p=0,002). Rekürrens olmayan hastalarda epilepsi görülmezken, tek rekürrens olanlarda %4,8, iki rekürrens olanlarda %42,1, üç ve daha fazla rekürrens olanlarda ise %100 oranında epilepsi geliştiği görüldü (p<0,001). Profilaktik rektal DZP tedavisi sonrası rekürrens sayısı arttıkça epilepsi gelişme riskinin arttığı görüldü.

Sonuç: Rekürrens sayısı azaldıkça epilepsi görülme sıklığının azalması ve rekürrens olmayan hastaların hiçbirinde epilepsi görülmemesi, dikkat çekici bir bulgu olarak göze çarpmaktadır. Ancak rektal DZP proflaksisinin epilepsi gelişimi üzerine kesin etkisinin anlaşılabilmesi için geniş ölçekli prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Febril Konvülziyon, Epilepsi, Aralıklı Rektal Diazepam, Profilaksi, Çocuk

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Introduction

Febrile seizure (FS) is the most common neurological disorder in childhood. FS was defined by International League Against Epilepsy as "seizures occurring in childhood after the age of 1 month, usually between 3 months and 6 years that are associated with a febrile illness, not caused by central nervous system (CNS) infection, without previous neonatal or unprovoked seizure and not meeting the criteria for other acute symptomatic seizures" (1).

The incidence of FS is between 2-5% in children aged 6 months to 5 years, and it peaks at 18 months (2,3). Approximately 50% of the first FS episode in children occurs in the second year of life, and the frequency of the first episode decreases before 6 months and after 3 years of age (4). Although the prognosis of FS is quite good, approximately 25-40% have a second FS, half of this group has a third FS, and 9-17% have more than three FS (5,6). While the incidence of epilepsy in the general population is 0.5-0.8%, this rate in FS varies between 2-10% in various studies. The risk of epilepsy has been reported to be 1-2% in simple FS, 4-7% in complex FS, and 30% in febrile status epilepticus (7-9).

The treatment of FS can be categorized into "acute" and "prophylactic" treatment. The main goal of acute treatment is to stop the seizure. Prophylactic treatment can be achieved through two methods: Long-Term Antiepileptic Treatment and Short-Term Intermittent Treatment during the febrile period. For Short-Term Intermittent Treatment during the febrile period, it is recommended to administer rectal diazepam (DZP) at a dose of 0.5 mg/kg every 12 hours when the body temperature is above 37.5 ^{o}C for the first 2 days of illness.

In the studies conducted so far, it has been argued that prophylactic rectal DZP treatment prevents the recurrence of FS (6,10,11), especially in patients with risk factors, but has no effect on subsequent epilepsy.

In this study, we aimed to investigate the rate of recurrence of FS and subsequent epilepsy in children who received intermittent prophylactic rectal DZP treatment.

Materials and Methods

Patients and Data Collection

The study included patients who were diagnosed with FS and given intermittent prophylactic rectal DZP treatment between 1 January 2005 and 1 December 2013 in Ankara University Child Hospital, Clinic of Pediatric Neurology (Ankara, Türkiye). We included the patients met the following conditions: no history of unprovoked seizures and continuous antiepileptic treatment, normal psychomotor development and an age between 6 months and 5 years. Data from 774 out of 839 patients diagnosed with FS were accessed, and 229 patients who received intermittent prophylactic rectal DZP treatment were analyzed retrospectively. In this study, we documented the demographic and clinical characteristics of the patients, the number of FS recurrences before and after intermittent prophylactic rectal DZP treatment, and whether epilepsy developed in the follow-up.

Definitions

FS was diagnosed as a seizure associated with a febrile illness, not caused by CNS infection, without previous neonatal or unprovoked seizure and not meeting the criteria for other acute symptomatic seizures. Simple FS is defined as generalized, lasting less than 15 minutes, comprised of generalized tonic and clonic activity without a focal component and recurrence within 24 hours or the same febrile illness. Complex FS is defined as exhibiting one or more of the following features: 1) partial-onset or focal features; 2) prolonged duration of more than 15 minutes; 3) recurrent FS within 24 hours of the first episode; and 4) association with postictal neurological abnormalities (9). Epilepsy was defined as the occurrence of at least two episodes of a FS's in two different days. The analysis could not include the details about the type of epilepsy. The analysis could not include the details of DZP prescription (dosage, timing, etc.) for each patient, but intermittent prophylactic DZP treatment protocol of our center is to administer rectal DZP at a dose of 0.5 mg/kg every 12 hours when the body temperature is above 37.5 ^{o}C for the first 2 days of illness.

Statistical Analysis

In this study, statistical analyzes were performed using SPSS Statistics 20.0 statistical package program. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether they are normally distributed. Descriptive statistical analysis methods were used to evaluate demographic and clinical data. Where appropriate mean, standard deviation, and median (minimum value-maximum value) were calculated for numeric variables. Frequency tables were used to describe categorical data. Categorical variables were compared by chi-square test and Fisher's exact test where appropriate. Mann-Whitney U test or independent samples t-test was used to compare two independent samples. One-way ANOVA or Kruskal-Wallis tests were used for 3-group comparisons. The Spearman Correlation Coefficient was used to investigate the relationship between continuous variables. The p-values obtained in the test results were evaluated at the 95% confidence level and the α=0.05 significance level.

Ethical Consideration

The study protocol was approved by the Non-Interventional Clinical Researches Ethics Board of Ankara University (approval

no: 17-738-14, date: 27.10.2014), and written informed consent was provided by the patients' parents and by patients aged >10 years. The study was conducted in accordance with the Helsinki Declaration.

Results

Patient Characteristics

The study included 229 children (141 males and 88 females) who received rectal DZP prophylaxis. The median age at the first FS episode was 18 months (range 6-60). 22% of the patients were under 12 months, 54% were under 18 months, 75% were under two years old and 89% were under three years of age. The median follow-up duration was 4.4 years (range 2.1-9.3 years). During the follow-up, 57 patients (24.9%) experienced one or more recurrences of FS, while subsequent epilepsy was observed in 26 patients (11.4%). Other clinical characteristics of the patients are shown in Table 1.

Recurrence of FS after Prophylactic Rectal DZP Treatment

Recurrence of FS was observed in 57 patients (24.9%) after prophylactic rectal DZP treatment. Of 57 patients with recurrence, 21 (36.8%) had one recurrence, 19 (33.3%) had two recurrences, and 17 (29.9%) had three or more recurrences. Recurrence of FS after rectal DZP prophylaxis was observed in 36.4% of females and 17.7% of males (p=0.002). The rate of recurrence after rectal DZP prophylaxis is 38.6% in patients with complex seizures and 20.3% in patients with simple seizures (p=0.006). There was no statistically significant difference in the rate of recurrence of FS after rectal DZP prophylaxis based on the age at the first seizure, family history of FS, and family history of epilepsy (p=0.36, p=0.51, and p=0.39, respectively) (Table 2). Our study also found that there was no statistically significant difference in the number of recurrences of FS after prophylactic rectal DZP treatment based on gender, age at the first seizure, seizure type, family history of FS, or family history of epilepsy (p=0.61, p=0.50, p=0.66, p=0.85 and p=0.61, respectively) (Table 3).

When the number of recurrences after prophylactic rectal DZP therapy in our study was examined, one recurrence was observed in 36.8% of patients, two recurrences in 33.3%, and three or more recurrences in 29.9%. When the seizure type of patients was examined, 3 or more recurrences were observed in 25.7% of patients who had simple FS, and in 36.4% of patients who had complex FS. Although it was found that the number of recurrences after prophylactic rectal DZP therapy was higher in patients with complex FS, this difference was not statistically significant.

Subsequent Epilepsy after Prophylactic Rectal DZP Treatment

During the follow-up, epilepsy occurred in 11.6% of the patients (26/229) who received prophylactic rectal DZP treatment and in 45.6% of those (26/57) who experienced recurrence after prophylaxis (p<0.001). While the rate of epilepsy was 7.6% in those with simple seizures, this rate was

Table 1: Demographic and clinical characteristics of patients with FS (n=229)

Gender, n (%)	**Female**	88 (38.4%)
	Male	141 (61.6%)
Age at first FS, months, median (range)		18 (6-60)
Follow-up duration, years, median (range)		4.4 (2.1-9.3)
Seizure type, n (%)	**Simple**	172 (75.1%)
	Complex	57 (24.9%)
Family history of FS, n (%)	**Yes**	88 (38.4%)
	No	141 (61.6%)
Family history of epilepsy, n (%)	**Yes**	36 (15.7%)
	No	193 (84.3%)
Number of recurrences before prophylactic treatment, n (%)	**1**	19 (8.3%)
	2	109 (47.6%)
	3	71 (31%)
	4	22 (9.6%)
	5	8 (3.5%)
Recurrence of FS after prophylactic treatment, n (%)	**Yes**	57 (24.9%)
	No	172 (75.1%)
Subsequent epilepsy after prophylactic treatment, n (%)	**Yes**	26 (11.4%)
	No	203 (88.6%)
Time to subsequent epilepsy, months, median (range)		24 (2-84)

FS: Febrile seizure

Table 2: Comparison of patients in terms of recurrence after prophylactic diazepam treatment

		Recurrence of FS after prophylactic treatment		
		Yes (n=57)	**No (n=172)**	**p-value**
Gender	**Female**	32 (36.4%)	56 (63.6%)	0.002
	Male	25 (17.7%)	116 (82.3%)	
Age at first FS, months, median (range)		18 (6-46)	18 (6-60)	0.364
Seizure type	**Simple**	35 (20.3%)	137 (79.7%)	0.006
	Complex	22 (38.6%)	35 (61.4%)	
Family history of FS, n (%)	**Yes**	24 (27.3%)	64 (72.7%)	0.510
	No	33 (23.4%)	108 (76.6%)	
Family history of epilepsy, n (%)	**Yes**	11 (30.6%)	25 (69.4%)	0.392
	No	46 (23.8%)	147 (76.2%)	

FS: Febrile seizure

22.8% in those with complex seizures (p=0.002). Epilepsy did not occur in patients without recurrence, while the rate of epilepsy was 4.8% in patients with one recurrence, 42.1% in those with two recurrences, 100% for three or more recurrences (p<0.001) (Table 4). In patients with epilepsy, it was shown that 3.8% of patients had one relapse, 30.8% had two relapses, and 65.4% had three or more relapses after prophylactic rectal DZP treatment (p<0.001). Consequently, as the number of recurrences increases after rectal DZP prophylaxis, the rate of epilepsy increases.

Discussion

FS are common in children and are generally considered to have a favorable prognosis. Some studies suggest that prophylaxis may not be necessary due to the overall good prognosis of FS. However, many other studies have demonstrated that prophylactic treatment can effectively prevent recurrence, particularly in patients with higher risk for epilepsy (6,10,11). It's worth noting that while prophylactic rectal DZP treatment has been shown to prevent recurrent FS, there is limited evidence to suggest that it can also prevent the development of epilepsy in the long term (9,12).

Of 229 patients who were started on prophylactic DZP treatment, 88 (38.4%) were female, and 141 (61.6%) were male. In previous studies, the male to female (M/F) ratio was found to be 1.2/1-1.4/1 (9,13), and in our study, the M/F ratio was found to be 1.6/1, similar to these results. It is known that it peaks in the 18th month and its incidence decreases after the age of 3 years (2,4,9). In our study, the median age of the first seizure was found to be 18 months, consistent with the literature.

Eighty-85% of children with FS have simple seizures, whereas 15% have complex seizures (9,13). In our study, it was observed that 172 (75.1%) of the patients had simple FS, and 57 (24.9%) had complex FS. The rate of patients with complex FS was found to be slightly higher than in the literature.

Family history of FS was reported to be 25-40% in patients with FS (14,15), and in our group, family history of FS was found to be 38.4%. Family history of epilepsy in patients with FS was found to be 10.3% in a previous study by Pavlidou et al. (16,17) and 8.8% in another study, and it was found to be higher with 15.7% in our study.

In our study, no recurrence was observed in 172 (75.1%) of the patients, while one or more recurrences were observed in

Table 3: Number of recurrences after prophylactic diazepam treatment

		Recurrence numbers after prophylactic diazepam treatment (n=57)			
		1 (n=21)	2 (n=19)	3 or more (n=17)	p-value
Gender, n (%)	Female	12 (37.5%)	12 (37.5%)	8 (25%)	0.619
	Male	9 (36%)	7 (28%)	9 (36%)	
Age at first FS (months) (range)		17 (7-30)	17 (8-42)	19 (6-46)	0.572
Seizure type	Simple	15 (42.9%)	11 (31.4%)	9 (25.7%)	0.669
	Complex	6 (27.3%)	8 (36.4%)	8 (36.4%)	
Family history of FS	Yes	13 (39.4%)	11 (33.3%)	9 (17.3%)	0.857
	No	8 (33.3%)	8 (33.3%)	8 (33.3%)	
Family history of epilepsy	Yes	3 (27.3%)	5 (45.5%)	3 (27.3%)	0.616
	No	18 (39.1%)	14 (30.4%)	14 (30.4%)	

FS: Febrile seizure

Table 4: Subsequent epilepsy after prophylactic diazepam treatment

		Subsequent epilepsy (n=26)		
		Yes	No	p-value
Gender	**Female**	11 (12.5%)	77 (87.5%)	0.666
	Male	15 (10.6%)	126 (89.4%)	
Age at first FS (month) (range)		18.5 (6-46)	18 (6-60)	0.865
Seizure type	**Simple**	13 (7.6%)	159 (92.4%)	0.002
	Complex	13 (22.8%)	44 (77.2%)	
Family history of FS	**No**	14 (9.9%)	127 (90.1%)	0.390
	Yes	12 (13.6%)	76 (86.4%)	
Family history of epilepsy	**No**	20 (10.4%)	173 (89.6%)	0.274
	Yes	6 (16.7%)	30 (83.3%)	
Number of recurrences after diazepam treatment	**1**	1 (4.8%)	20 (95.6%)	0
	2	8 (42.1%)	11 (57.9%)	
	3 or more	17 (100%)	0 (0%)	

57 patients (24.9%) after prophylactic rectal DZP treatment. In studies investigating the efficacy of prophylactic DZP treatment, recurrence rates after DZP prophylaxis were reported to be between 5% and 42% (17-23). The recurrence rate in our study was found to be among the rates reported in the literature.

When the patients were examined in terms of gender, recurrence was observed in 36.4% of girls and 17.7% of boys after rectal DZP treatment (p=0.002). Male gender is considered a minor risk factor for recurrence in patients who did not receive prophylaxis, and there is not yet a study investigating the effect of gender on recurrence in patients receiving prophylaxis (24).

When the patients were compared regarding seizure type, the recurrence rate was 38.6% in patients with complex FS, while this rate was 20.3% in patients with simple FS (p=0.006). In a study by Pavlidou et al. (16) on patients who did not receive prophylaxis, recurrence rates were found to be higher in patients with complex FS. In our study, as in many other studies (17,24-26), complex FS was thought to be a risk factor for FS recurrence.

A family history of FS is known as a definite risk factor, and a family history of epilepsy is known as a possible risk factor for FS recurrence (5,16,24,25,27). In our study, it was observed that 27.3% of the patients with a family history of FS and 23.4% of those without a family history of FS experienced recurrence after prophylactic treatment. In the study conducted by Pavlidou et al. (16), FS recurrence was significantly higher in patients with a family history of FS. In our study, while not statistically significant, there was a slightly elevated rate of recurrent episodes among patients who had a family background of FS.

Recurrence of FS was observed in 30.6% of patients with a family history of epilepsy and 23.8% of those without a family history of epilepsy. In the study of Pavlidou et al. (17), recurrence was observed in 41% of those with a family history of epilepsy and 40% of those without a family history of epilepsy, and no significant difference was found. In the study by Tarkka et al. (28) with patients who did not receive prophylaxis, recurrence was observed in 28% of patients with a family history of FS and in 22% of patients without a family history of FS; recurrence was seen in 38% of patients with a family history of epilepsy and in 22% of patients without a family history of epilepsy. In our study, although the recurrence rates were higher in patients with a family history of epilepsy compared to patients without a family history of epilepsy, no statistically significant difference was found.

In our study, subsequent epilepsy was diagnosed in 12.5% of girls and 10.6% of boys after prophylactic DZP treatment (p=0.66). Although there is no research investigating the effect of gender on subsequent epilepsy after prophylactic treatment, it is known that gender is not among the risk factors in studies investigating the development of epilepsy after FS in patients who did not receive prophylaxis (8,29-32).

When the age of the first seizure of patients was examined, the median age of the first seizure was 18.5 months for those who developed epilepsy and 18 months for those who did not. It is known that the age of the first seizure is not among the risk factors for the development of epilepsy in children who have had FS (8,24,29,33,34). In a retrospective study by Vestergaard et al. (35) in patients who did not receive prophylaxis, it was argued that there is an increased risk of developing epilepsy within two years after FS in children who experience their first FS below one year of age or above three years of age. Pavlidou et al. (32) argued in their study that the first FS occurring above three years of age doubles the risk of developing epilepsy. In our study, it was found that the age of the first FS did not affect the development of epilepsy in patients who received prophylactic DZP treatment.

When patients were analyzed according to the type of seizure, epilepsy was observed in 7.6% of those who had a simple FS and 22.8% of those who had a complex FS (p=0.002). While the risk of developing epilepsy in the general population is known to be 0.5-0.8%, the risk of developing epilepsy in simple FS is 1-2.2%, and in complex FS is 4.1-7% (33). According to the study conducted by Annegers, the risk of epilepsy is found to be 6-8% when one complex FS feature is present, 17-22% when two features are present, and 49% when three features are present. Some publications argue that focal seizures specifically increase the risk of epilepsy (29,32), but many other studies suggest that all three features of complex seizures increase the risk of developing epilepsy (7,8,33,36). In our study, similar to previous studies, it was supported that a history of complex FS is a risk factor for subsequent epilepsy.

When we evaluate the number of recurrences after prophylactic DZP treatment, it was found that epilepsy was diagnosed in 4.8% of patients who had one recurrence after treatment, 57.9% of patients who had two recurrences, and 100% of patients who had three or more recurrences. Notably, subsequent epilepsy did not occur in patients who did not have recurrences after prophylactic DZP treatment. In our study, out of the 26 patients who developed epilepsy, a substantial majority (65.4%) had three or more recurrences after DZP prophylaxis. Additionally, 30.8% had two recurrences, while only 3.8% had a single recurrence following DZP prophylaxis. In the study by Pavlidou et al. (32), among patients who did not receive DZP prophylaxis, it was reported that epilepsy occured in 10.4% of patients who had one recurrence, 17.9% of patients who had two recurrences, 22.9% of patients who had three recurrences and 25.8% of patients who had four or more recurrences. Other studies also support that the risk of developing epilepsy increases with the number of recurrences, as seen in the study by Berg and Shinnar (34), among patients who did not receive DZP prophylaxis, where epilepsy was observed in 4.2% of patients with one recurrence, 6.1% with two recurrences, 8.1% with three recurrences, and 20.4% with four or more recurrences. The studies conducted on patients not receiving prophylaxis also indicate an increased risk of epilepsy as the number of recurrences of FS increases, similar to our study. Taken together

with our results, this data shed light on the importance of monitoring and managing recurrences effectively to mitigate the potential development of epilepsy.

Study Limitations

The strength of our study is that it is the first study that reveals the outcomes of the patients who received intermittent rectal DZP prophylaxis in the Turkish pediatric FS cohort. The limitations of our study are its retrospective design, relatively short follow-up duration (i.e., 4.4 years), and relatively small-sized study group.

Conclusion

In our study, it was found that as the number of recurrences decreased, the rate of epilepsy also decreased, and patients without recurrence did not experience epilepsy. Although this interesting finding raises questions about whether reducing the number of recurrences can prevent the subsequent epilepsy, it is not possible to make a definitive interpretation with these results. Large scale prospective studies are needed to determine the preventive effect of prophylactic rectal DZP treatment on subsequent epilepsy.

Ethics

Ethics Committee Approval: The study protocol was approved by the Non-Interventional Clinical Researches Ethics Board of Ankara University (17-738-14, date: 27.10.2014).

Informed Consent: Written informed consent was provided by the patients' parents and by patients aged >10 years.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.D., Concept: G.D., Design: G.D., Data Collection and Processing: E.G.Ö., M.G.K., Analysis or Interpretation: E.G.Ö., M.G.K., G.Ö.T., G.D., Literature Search: E.G.Ö., M.G.K., G.Ö.T., G.D., Writing: E.G.Ö.

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