The use of flecainide in critical neonates and infants with incessant supraventricular tachycardias

"Incessant" supraventriküler taşikardili kritik yenidoğan ve süt çocuklarında flekainid kullanımı

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ABSTRACT

Objective: This study aimed to evaluate the efficacy of flecainide therapy in neonates and infants with drug resistant incessant supraventricular tachycardia.

Methods: The study included 11 neonates and infants who received medical and/or ablation therapy between January 2010 and December 2013. Mean patient age and weight were 101.6±96 days and 5.3±1.9 kg respectively. Of the 12 patients, 5 underwent ablation between January 2010 and December 2011, and 6 were treated medically between January 2012 and December 2013. Mean follow-up time was 18 months (6 months–4 years).

Results: The antiarrhythmic agent flecainide only became available in Turkey in 2012, and the most noteworthy point was its addition to the therapy administered prior to ablation (adenosine, esmolol-propranolol, propafenone, amiodarone and cardioversion). In all 6 patients admitted between January 2012 and December 2013, refractory SVT was successfully treated with the administration of a triple therapy regimen of esmolol-propranolol, amiodarone and flecainide. One patient with myocarditis developed an atrial flutter complicated by a concealed accessory pathway and was put on extracorporeal membrane oxygenation (ECMO) support due to cardiopulmonary failure. The SVT was terminated, but the patient died on the fifteenth day of ECMO support. One patient with recurrent tachycardia, who had previously undergone ablation for a complex cardiac anomaly and Wolf-Parkinson-White syndrome, was treated with ablation again. No recurrence of tachycardia was observed in any of the other 9 patients.

Conclusion: It appears that the use of propranolol-esmolol and amiodarone combined with flecainide in the medical treatment of drug-resistant SVT may reduce the need for ablation in critical neonates and infants.

ÖZET

Amaç: Bu çalışmanın amacı, ilaca dirençli sürekli supraventriküler taşikardili yenidoğan ve süt çocuklarında flekainid tedavisinin etkinliğini değerlendirmektir.

Yöntemler: Çalışmaya, Ocak 2010-Aralık 2013 tarihleri arasında merkezimizde tıbbi ve/veya ablasyon tedavisi uygulanan, geriye dönük olarak değerlendirilen 11 yenidoğan ve süt çocuğu alındı. Hastaların ortalama yaşı 101.6±96 gün, vücut ağırlığı 5.3±1.9 kg idi. Tüm hastalardan 5'ine Ocak 2010 ile Aralık 2011 tarihleri arasında ablasyon uygulandı, hastaların 6'sı Ocak 2012 ile Aralık 2013 tarihleri arasında tıbbi tedavi edildi. Takip süresi 18 ay (6 ay–4 yıl) oldu.

Bulgular: Ablasyon yapılan hastalara tıbbi tedavi olarak adenozin, esmolol-propranolol, propafenon, amiodaron ve kardiyoversiyon tedavileri uygulandı, ancak dikkat çekici olarak son iki yıllık dönemde ülkemizde flekainid bulunabilmesi nedeniyle bu ilaç tedaviye eklendi. Son iki yıllık dönemde başvuran 6 hastanın hepsinde esmolol-propranolol, amiodarone ve flekainid içeren üçlü tedavi ile dirençli SVT'ler kontrol altına alındı. Miyokardit tanılı hastada atriyum flatteri ile gizli aksesuvar yol birlikte görüldü ve kardiyopulmoner yetersizlik nedeniyle ECMO'ya (ekstrakorporeal membran oksijenasyon) alındı. SVT'si kontrol edilebilmesine rağmen, hasta 15. günde ECMO'dan çıkamadan kaybedildi. Taşikardi nüksü olan hastaya ise kompleks kalp anomalisi ve Wolf-Parkinson-White sendromu nedeniyle ablasyon yapılmıştı ve ablasyon tekrar başarılı oldu. Kalan 9 hastada taşikardi nüksü görülmedi.

Sonuç: Yenidoğan ve infantların dirençli SVT'lerinin tıbbi tedavisinde propranolol-esmolol ve amiodarone ile birlikte flekainidin kombine kullanımı sayesinde, ablasyon gereksinimi azaltılabilir gibi görünmektedir.

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Supraventricular tachycardia (SVT) is the most common type of tachyarrhythmia seen in pediatric patients, and accounts for more than 90% of pediatric arrhythmias. Symptoms vary according to age, heart rate and duration of tachycardia, and neonates and infants may be admitted with congestive heart failure findings.[1]

The natural history of SVT in most neonates and infants includes resolution by one year of age.[1,2] Pharmacologic therapy is generally used to suppress the tachycardia until spontaneous resolution occurs, but in some cases SVT cannot be managed with first-line antiarrhythmic agents. Traditional medical therapy for SVT in neonates and infants consists of adenosine, propranolol, esmolol and digoxin, administered alone or in combination. In patients resistant to initial treatment, Class IC and Class III agents (amiodarone, sotalol, propafenone, and flecainide) are preferred as second- and third-line therapy.[1–4] Flecainide acetate is a relatively new benzamide-derived drug that has proven to be more effective than most other drugs in the treatment of SVT and ventricular tachycardia (VT) in adult patients, and it is increasingly being used with success in pediatric patients.[4–7] Intravenous flecainide is unavailable in Turkey, while the oral form has only been available at limited locations since 2012.

In most neonates and infants, SVT is managed with antiarrhythmic treatment, and ablation can be performed when the infants reach a sufficient age and weight. Today, most centers avoid transcatheter ablation for resistant SVT in neonates and infants until all other options have been exhausted. In cases where medical treatment fails and/or is complicated by ventricular dysfunction, ablation can be life-saving.[8–10]

METHODS

This retrospective study included 11 neonates and infants (<1 year of age) who received medical (n=6) and/or ablation (n=5) therapy at our center between January 2010 and December 2013. Enrolled in the study were SVT patients resistant to first-line treatment (adenosine, digoxin, propranolol-esmolol and cardioversion). Patients with tachycardia exclusively associated with cardiac surgery were excluded from the sample. All types of treatment were administered in the intensive care unit. The diagnosis and differentiation of SVT were made using 12-lead electrocardiography (ECG), 24-hour Holter monitoring, adenosine, and/or transesophageal-transvenous electrophysiology study. Patients with tachycardia-related hypotension and cardiac insufficiency findings were put on inotropic support (dopamine, milrinone, adrenaline) until SVT was terminated. Echocardiography was performed prior to therapy to assess anatomy as well as ventricular size and function.

Abbreviations:

ECG	*Electrocardiography*
ECMO	*Extracorporeal membrane oxygenation*
RFA	*Radiofrequency ablation*
SVT	*Supraventricular tachycardia*
TCA	*Transcatheter cryoablation*

Class Ic and III antiarrhythmic agents were used a second-and/or third-line therapy in patients resistant to first-line treatment agents. In patients who were all drug-resistant or had ventricular dysfunction, radiofrequency ablation (RFA) or transcatheter cryoablation (TCA) was performed. Notably, the class Ic agent administered to the 5 patients in the first 2-year period was propafenone, while in the second 2-year period 6 patients were put on oral flecainide, which had only then become available in Turkey. Response to treatment was monitored with 24-h Holter monitoring and telemetry. Efficacy was defined as no clinical tachycardia detected at outpatient follow-up examinations on ECG and 24-hour Holter monitoring.

The study was approved by the Ethics Committee of our hospital, and all the patients provided written informed consent.

RESULTS

Clinical characteristics of patients

The clinical features and cardiac statuses of all patients are summarized in Table 1. Mean patient age was 3.4±3.2 months (range: 12 days-9.5 months) and mean body weight was 5.3±1.9 kg (range: 3–9 kg). As for clinical presentation, 4 patients had cardiogenic shock, 4 had cardiac insufficiency, 1 was delivered after a pregnancy with fetal tachycardia, 1 (with corrected transposition great arteries) had pulmonary hypertension and cardiac insufficiency with a deteriorating general condition, and 1 was hemodynamically stable, but was found to have tachycardia on physical examination. Antiarrhythmic treatment was started after intubation in 5 cases, 3 patients were started on drugs first and were later intubated after their general condition deteriorated in follow-up, and 3 patients did

Table 1. Clinical features and cardiac statuses of all patients

Patient no	Age (day)	Sex	Weight (kg)	Initial presentation	Diagnosis	TCL (msec) use time (hour)	Inotrophic agents and	Echocardiographic findings	LVDd (mm)	FS (%)
The first two years										
1	25	Male	4.5	Cardiogenic shock	AVRT	260	M 103 D 96 A 57 N 92	PFO	27 (14–23)	23
2	285	Female	9	Referred patients with tachycardia heart failure	PJRT	330	None	VSD	33 (20–29)	26
3	12	Male	4		PJRT	320	D 48 N 3	PFO	26 (14–23)	22
4	22	Female	3.5	Cardiogenic shock	AVRT	250	D 43 A 39	PFO	29 (14–23)	20
5	150	Male	6	Pulmonary hypertension, heart failure	WPW/ AVRT	260	D 98	c-TGA, VSD, hypoplastic RV, PFO, PH	23 (18–27)	30
The last two years										
1	240	Male	8.8	Heart failure	PJRT	306	None	MR	26 (22–31)	28
2	49	Female	5.2	Cardiogenic shock	PJRT	240	M 65 D 62	PFO, MR	22 (18–25)	23
3	69	Female	5	Cardiogenic shock	AVRT	207	M 91 D 74 A 45	MR, AR	24 (19–27)	25
4	59	Male	4.6	Heart failure	AVRT	210	M 117 D 117	PFO, VSD, MR	20 (18–25)	30
5	180	Male	5.6	Heart failure	AVRT	225	None	HCMP	26 (19–26)	39
6	27	Male	3	Fetal tachycardia	Atrial Flutter, AVRT	316	M 468 D 460 A 447 N 174	PDA, MR, ASD	22 (16–21)	20

A: Adrenaline; AR: Aortic regurgitation; ASD: Atrial septal defect; AVRT: Atrioventricular reciprocating tachycardia; c-TGA: Corrected transposition of great artery; D: Dopamine; E: Esmolol; FS: Fractional shortening; HCMP: Hypertrophic cardiomyopathy; LVDd: Left ventricle end diastolic diameter; M: Milrinone; MR: Mitral regurgitation; Msec: Milliseconds; N: Noradrenaline; PDA: Patent ductus arteriosus; PFO: Patent foramen ovale; PH: Pulmonary hypertension; PJRT: Permanent form of junctional reciprocating tachycardia; RV: Right ventricle; TCL: Total cycle length; VSD: Ventricular septal defect; WPW: Wolff-parkinson-white syndrome.

not require mechanical ventilation. In the echocardiographic assessment, mean left ventricular end-diastolic diameter in patients treated with ablation was 27.6±3.7 mm and in those given medical therapy 23.3±2.4 mm, while fractional shortening was 24%±4 and 28%±7 respectively. Two patients had a ventricular septal defect, 1 a patent ductus arteriosus, 1 hypertrophic cardiomyopathy, 1 a complex cardiac anomaly (corrected transposition of the great arteries, ventricular septal defect, right ventricular hypoplasia and pulmonary hypertension), while 6 patients had a patent foramen ovale.

SVT management and response to therapy

Diagnosis, follow-up and therapy features of all patients are summarized in Table 2. The inotropic agents used were milrinone, dopamine, adrenaline and noradrenaline. Two patients did not receive inotropic support. The most frequently and longest used ones were milrinone and dopamine, and the average duration of inotropic support in most cases was 2–4 days (Table 1).

In the first 2 years of the 4-year study period, 5 patients required ablation therapy,[11] while the 6 patients admitted in the second half of the study period were treated with antiarrhythmic agents. The duration of therapy until tachycardia was successfully terminated varied from patient to patient, ranging between 30 and 44 hours (Table 2). Most noteworthy in this study was the use of the Class Ic agent flecainide in the therapy administered prior to ablation (adenosine, esmolol-propranolol, propafenone, amiodarone and cardioversion) when it became available in Turkey during the latter years of the study. Drug-resistant SVT was terminated with a triple therapy regimen of esmolol-propranolol, amiodarone and flecainide in all 6 of the patients admitted in the last two years (Table 2).

Table 2. Diagnosis, follow-up and therapy features of all patients

Patient no	Diagnosis	TEEPS/TVEPS	ICU time (day)	MV time (day)	Antiarrhythmic management	Ablation indication	Tachycardia control time (hour)	Follow up duration (months)	Outcome
The first two years									
1	AVRT	TVEPS	4.4	2.7	Ad, CV, E, A, P	LVD,RA	41 (with ablation)	25	Alive, NSR
2	PJRT	TVEPS	3.5	0	Ad, A, P	LVD, RA	330 (with ablation)	25	Alive, NSR
3	PJRT	TVEPS	4.0	0.5	A, Ad, E, P	LVD, RA	19 (with ablation)	25	Alive, NSR
4	AVRT	TVEPS	3.1	0.5	Ad, CV, A, P	LVD, RA	43 (with ablation)	40	Alive, NSR
5	WPW/AVRT	TVEPS	6.0	2.1	Ad, CV, E, A, P	RA	44 (with ablation)	27	Alive, NSR
The last two years									
1	PJRT	Negative	0	0	Ad, CV, Prop, E, A, F	Absent	168	12	Alive, NSR
2	PJRT	Negative	2.6	0	Ad, CV, Prop, A, F	Absent	31	8	Alive, NSR
3	AVRT	TEEPS	8.8	7	Ad, CV, E, A, F	Absent	34	7	Alive, NSR
4	AVRT	Negative	4.9	0	Ad, CV, E, A, F	Absent	74	6	Alive, NSR
5	AVRT	Negative	0	0	Ad, CV, Prop, A, F	Absent	37	8	Alive, NSR
6	Atrial Flutter, AVRT	TEEPS	20	20	Ad, CV, D, E, A, F	Absent, Ex after 15 days at the ECMO	230	–	Death

A: Amiodarone; Ad: Adenosine; AVRT: Atrioventricular reciprocating tachycardia; CV: Cardioversion; D: Diltiazem; E: Esmolol; ECMO: Extracorporeal membrane oxygenation; F: Flecainide; ICU: Intensive care unit; LVD: Left ventricular dysfunction; Met: Metoprolol; MV: Mechanic ventilation; NSR: Normal sinus rythm; TEEPS: Transesophageal electrophysiologic study; TVEPS: Transvenous electrophysiologic study; P: Propafenone; PJRT: Permanent form of junctional reciprocating tachycardia; Prop: Propranolol; RA: Refractory to antiarrhythmic drugs; TCL: Total cycle length; WPW: Wolff-parkinson-white syndrome.

Follow-up

Mean follow-up time was 18.3 months (range: 6 to 40 months). Death occurred in 1 patient during follow-up, and 1 had recurrent tachycardia. The patient with myocarditis developed atrial flutter complicated by concealed accessory pathway and was put on extracorporeal membrane oxygenation (ECMO) support due to cardiopulmonary failure. Although the SVT was terminated, the patient died on the 15th day of ECMO support. The patient with recurrent tachycardia, who had previously received ablation therapy for complex cardiac anomaly and Wolf-Parkinson-White (WPW), was treated with ablation again. No recurrence of tachycardia was observed in any of the other 9 patients, 4 of whom were followed up without drugs, while 5 used flecainide, propranolol and amiodarone during the 1-6 month follow-up period (Table 2). There were no instances of proarrhythmia, no severe side effects and none of the patients required a pacemaker.

DISCUSSION

Supraventricular tachycardia in infancy is sometimes difficult to manage with traditional first-line antiarrhythmic agents. Several pharmacologic regimens have been proposed for the management of refractory SVT, including Class Ic and Class III agents as monotherapy or in combination with digoxin and/or propranolol.[3–6] When SVT is refractory to pharmacologic therapy and/or complicated by ventricular dysfunction, RFA or TCA is used to eliminate the arrhythmia substrate in infants.[8–11] Our study was concerned with the efficacy of oral flecainide combined with amiodarone and esmolol-propranolol in preventing arrhythmic activity and reducing the need for ablation in critical neonates and infants. All rhythm disorders in our patients were long-standing and had lead to ventricular dysfunction and cardiomyopathy. Interestingly, the combination of esmolol-propranolol, amiodarone and propafenone was not effective. In these 5 patients from the first years of the study, left ventricular dysfunction progressed and ablation had to be performed. Meanwhile, in the 6 patients who were started on flecainide in the last 2 years, tachycardia was eliminated, progress of ventricular dysfunction ceased and functions returned to normal. Despite the small sample size, these promising results have led us to think that combining beta blockers and amiodarone with flecainide instead of propafenone may be effective in eliminating tachycardia and reducing the necessity for ablation in patients with incessant SVT.

In one of the largest sample studies of SVT management in neonates and infants, Weindling et al. reported a 70% success rate in 112 cases of SVT treated with digoxin and/or propranolol, particularly in cases of atrioventricular reentrant tachycardia or atrioventricular nodal reentrant tachycardia.[3] In the remaining 30% of patients (n=31), Class I or Class III agents were required to suppress SVT. While there was no mortality, morbidity or severe side effects in this study, 7 patients required ablation. In cases where propranolol and/or digoxin had no effect, Class III agents (amiodarone, sotalol) were reported to be more effective as second-line therapy and were recommended over Class I agents. Only flecainide was used as a Class Ic drug in the study.[3] In one of the notable studies on combined antiarrhythmic treatment of persistent SVT in infants, Fenrich et al. reported that 9 infants with an average age of 2 months were treated unsuccessfully with flecainide and amiodarone individually, while a combination of the two yielded a 78% success rate and no severe side effects.[5]

Two major recent studies in the area of combination therapy, Drago et al. and Akin et al., report a 80-92% success rate for amiodarone combined with propranolol for treatment of tachycardia.[12,13] At our center we also prefer to start with propranolol-esmolol and amiodarone in cases of persistent SVT. However, while this approach is generally successful with children, it failed with the 11 neonates and infants we reported in this study, necessitating ablation in 5 patients with cardiac insufficiency refractory to inotropes. In the 6 cases in which we were able to use flecainide as third-line therapy, there was no need for ablation. In the study by Akin et al. 60% of patients had normal ventricular function and hemodynamics at start of therapy, mean patient age was older and success was defined as suppressing tachycardia in the first 2-month period.[13] Almost all of our patients, in contrast, had abnormal hemodynamics, borderline ventricular dysfunction and needed inotropic support. For this reason, in critical cases refractory to propranolol-esmolol and amiodarone, we added flecainide hoping to avoid ablation.

The efficacy of flecainide in the treatment of accessory pathway reentrant SVTs in adults and chil-

dren is reported in a small series.[5–7] Flecainide slows down conduction in atrioventricular node and accessory pathways and increases the cycle and refractory period durations of antegrade and retrograde accessory pathways. It has been used as a second-line agent, most often intravenously, with a loading dose to terminate the arrhythmia followed by oral maintenance dosage. However, studies have shown that oral usage of flecainide as monotherapy or combined with sotalol-amiodarone is effective in infants.[4–6,14,15] Higher doses may be needed initially in some patients in order to eliminate tachycardia by slowing down conduction. As amiodarone may increase flecainide plasma levels by ≈ 30%, it is recommended to decrease the initial daily dose of flecainide by 20% to 50%.[4,5,16] We have reported our experience with medium dosage of oral flecainide (50–75 mg/m^2/day) and the good response we observed in a small group of patients. No side effects occurred that would necessitate discontinuing therapy.

Study Limitations

This study is limited by the inherent nature of a retrospective study involving a small group of patients due to the rare prevalence of the disease. A larger study would be required in order to more conclusively validate the use of oral flecainide. Non-availability of drug level monitoring has also been a limitation of this study.

Conclusion

Although the present study had a small sample size, the observed results are encouraging. For the neonate and infants reported here, combined propranolol-esmolol, amiodarone and flecainide therapy appeared to be safe and effective for eliminating refractory SVT. This combination may reduce the need for ablation in critical neonates and infants.

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Anahtar sözcükler: Kateter ablasyonu; flekainid; supraventriküler taşikardi; süt çocuğu.