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Review Article

Evaluating antiarrhythmic drugs for managing infants with supraventricular tachycardia; a review

Azad Mojahedi[1], Afsaneh Mirshekari[2]

[1]*Department of Internal Medicine, Stony Brook University Hospital, Stony Brook, New York, The United States;*
[2]*Department of Pediatrics, Zabol University of Medical Sciences, Zabol, Sistan and Baluchestan, Iran*

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Abstract: Supraventricular tachycardia (SVT) is the most prevalent arrhythmia observed in infants, impacting individuals with or without congenital cardiac dysfunction. Infantile-onset SVT typically manifests within the initial one to two months of life. A variety of anti-arrhythmic medications are employed to treat SVT in infants during their first year of life. Nevertheless, a consensus has yet to be reached on the most efficacious drug, and treatment approaches continue to vary considerably As SVT remains a frequent problem around the world, with different management approaches and no obvious optimal option, we conducted a systematic review of the new update of antiarrhythmic drugs for managing SVT in infants under one year old.

Keywords: Antiarrhythmic, supraventricular tachycardia, infants

Introduction

Supraventricular tachycardia (SVT) is an irregular electrical activity in the upper portion of the heart that causes an abnormally rapid cardiac rhythm [1, 2]. It typically manifests as a narrow QRS complex and arises above the ventricles; atrial flutter and fibrillation are typically excluded from the diagnostic criteria [3]. Sometimes, SVT is referred to by other names, such as paroxysmal supraventricular tachycardia (PSVT) or paroxysmal atrial tachycardia (PAT), which means the heart rate suddenly increases and decreases. The most prevalent form of SVT among adolescents is Wolff-Parkinson-White syndrome (WPW) [4, 5]. SVT is rarely fatal, and treatment outcomes are exceptionally favorable. SVT is characterized by symptoms of an irregular heartbeat, including weakness, chest pain, dizziness, shortness of breath, and/or fainting. The episodes may be associated with physical activity. Although the SVT configuration is frequently present from birth, symptoms might appear at any time. Consequently, there is a 50% chance that the SVT will occur again in an older child [6, 7].

Infantile-onset SVT typically manifests within the initial one to two months of life and is frequently attributed to orthodromic reciprocating tachycardia caused by an accessory pathway. By the age of one year, most patients experience resolve of clinical episodes [8, 9]. Recurrence rates may be greater for atypical presentations, including episodes occurring after the infant's first few months. Untreated SVT has the potential to result in cardiomyopathy and cardiac failure [10]. SVT in neonates may be identified through the manifestation of symptoms consistent with congestive heart failure. For several hours, a baby's heart rate can be kept extremely high without causing any symptoms. If the episode continues for more than 24 to 36 hours, the muscle of the heart begins to slow down and pump with a decreasing amount of effort [11]. Symptoms include insufficient eating, excessive drowsiness, irritability, diarrhea, rapid breathing, and/or pale skin color [12]. Acute care for an infant with SVT can be difficult because the actual cause of the tachycardia is often unknown. The treatment strategy is determined by the patient's presentation and clinical status, so SVT is critical and must be treated [13].

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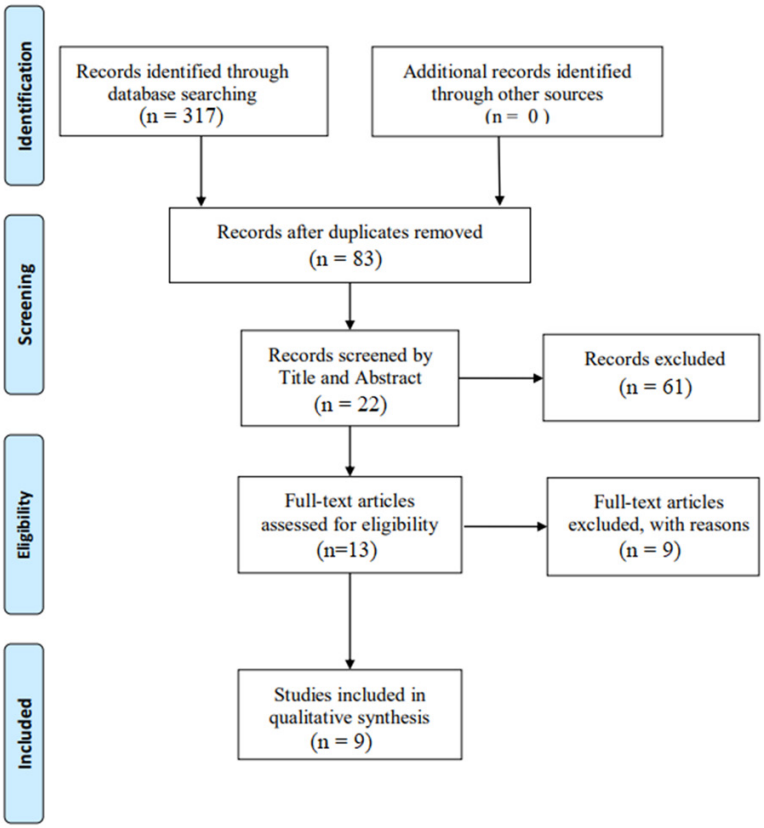

Figure 1. PRISMA flow diagram for enrollment of studies.

Adenosine and vagal maneuvers are two current treatments for acutely terminating an SVT episode. Antiarrhythmic drugs, on the other hand, are utilized immediately when those maneuvers fail, as well as prophylactic or maintenance therapy. However, vagal maneuvers and adenosine are conventional first-line therapies, and the decision on which medicine to add acutely or for chronic maintenance varies greatly [13]. Drugs such as flecainide, amiodarone, propranolol, and digoxin are frequently prescribed to infants with SVT. Unlike controlled trials, management decisions are founded upon experiential factors, including institutional practice and physician preference. However, limited investigations evaluate the safety and efficacy of antiarrhythmic drugs for the control of SVT in infants [13, 14].

As SVT remains a frequent problem around the world, with different management approaches and no obvious optimal option, we conducted a systematic review of the new update of antiarrhythmic drugs for managing SVT in infants under one year old.

Material and methods

Search strategy

We have conducted a literature review of the antiarrhythmic drugs for managing infants with SVT. The research was performed in compliance with the PRISMA criteria, Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and the Flow Diagram is shown in **Figure 1**. The research was conducted in the PubMed, MEDLINE, Scopus, Web of Science, DOAJ, Science Direct, and Google Scholar databases between January 2019 and October 2023. It used the Advanced Search Builder, and the keywords were searched in [Title OR Abstract]. We have filtered only research articles published in the English language and using the terms '(Supraventricular tachycardia [Mesh]) AND (Infant [Mesh] OR Neonate [Mesh] OR Newborn [Mesh]) AND (Antiarrhythmic Drug [Mesh])'.

Inclusion and exclusion criteria

Original articles that evaluated the new update of antiarrhythmic drugs for managing SVT in infants under one year old were eligible for inclusion in the systematic review. References in the selected research were reviewed for other relevant literature. Case reports and series involving a limited number of patients, review articles lacking original data, editorials, letters, and conference papers were all excluded. Also, investigations that include patients who had undergone cardiac surgery, were excluded.

Data extraction and quality evaluation

A.F. reviewed titles and abstracts. After implementing inclusion and exclusion criteria, data from studies were extracted based on the survey's requirements.

After scanning the references in previously published review articles, any relevant studies were included. We obtained 9 eligible published research articles in their final version. For some of them, we chose to include only the main findings that fit the purpose of this review. Data extraction tables based on the final articles' data are shown in **Table 1**.

According to the studies that have been conducted, there are no specific guidelines for treating SVT in infants. In fact, although adenosine and propranolol are often used for the pharmacological treatment of SVT in infants, however, these drugs may not be standard treatment for all infants. Therefore, the use of other drugs has become common for the management of SVT. On the other hand, very few review studies have been conducted in this regard. Our aim is to review different articles to evaluate the management of SVT with different drugs.

Discussion

The most prevalent type of arrhythmia in children is SVT, which is estimated to occur in between 0.1 and 0.4% of the pediatric population. In 50-60% of cases, the initial SVT episode happens in the first year of life, usually in the first three to four months [15].

The most prevalent type of paroxysmal SVT in pediatrics is atrioventricular re-entrant tachycardia (AVRT), caused by an accessory pathway. This category of tachycardia comprises 70-80% of all infant tachycardias. Atrioventricular nodal re-entrant tachycardia (AVNRT) is the second most prevalent form of tachycardia, occurring much less frequently in neonates (5-17%). The incidence of focal atrial tachycardia (FAT) in neonates with SVT ranges from 5 to 10% [2, 9, 16].

SVT can manifest as a singular, occasionally self-limiting episode or as persistent and long-lasting episodes that, in the absence of appropriate treatment, can result in significant morbidity, particularly among neonates and infants [8]. The most prevalent approach among clinicians is to administer prophylactic antiarrhythmic medications for a duration of 6 to 12 months following the diagnosis of a first episode of SVT in a neonate [17]. Interestingly, there is little clinical trial data regarding medical therapies, and there is no agreement or evidence for the best way to administer medication or how long to administer medicine. There have been recent suggestions that prophylactic antiarrhythmic treatment may be significantly reduced. An extensive array of antiarrhythmic medicines are administered to neonates and infants. Currently, the most frequently employed pharmaceuticals include digoxin, amiodarone, sodium-channel blockers (e.g., propafenone and flecainide), beta-receptor-blocking compounds, and sotalol [18, 19].

Overall, the prognosis for infant SVT is positive, as evidenced by the spontaneous resolution of at least 70% of cases by the age of one year. Infants have a 22-55% risk of SVT recurrence, which is significantly lower than that of older children [20]. Radiofrequency catheter ablation is only used in newborns with severe and drug-resistant tachycardias, as the technique has a lower success rate and higher problems in this age group. Elective catheter ablation is a well-proven technique with good outcomes for children above 15 kg and four years old with persistent symptomatic SVT [21, 22].

Although a variety of anti-arrhythmic medications are employed to treat SVT in infants during their first year of life, nevertheless, a consensus has yet to be reached on the most efficacious drug, and treatment approaches continue to vary considerably. The pharmacological therapy for infant SVT is predominantly determined by retrospective studies and physician experience [14, 19]. It is challenging to conduct trials with adequate power to identify statistically significant differences in therapy efficacy among infant SVT due to the limited number of cases and the wide array of antiarrhythmic therapies available [23]. To overcome this constraint, we performed a systematic review in which we gathered recently published articles on infant SVT and collected a substantial study population for the purpose of analysis (**Table 1**).

Review of studies conducted on the pharmacological management of SVT

In 2021, Capponi et al. [24] assessed the best medicine for treating SVT in infants. Among 55 infants, 45 cases had re-entry tachycardia, and 10 cases had automatic tachycardia. In patients with re-entry tachycardia, flecainide

Table 1. Characteristics of the included articles evaluating the pharmacological management of infant SVT

Study	Year	Study type	Study population	Mean of age, day ± SD (IQR)	Gender, male (%)	Type of SVT	Antiarrhythmic drugs and dosage	Treatment duration	Follow-up (Months/ years)	Total number of complications	Conclusion
Capponi et al.	2022	Retrospective study	55	12.5 (1-303)	N/A	Automatic tachycardia, AVRT, AVNRT, PJRT	Flecainide: 50 to 120 mg/m^2/day (Oral) Nadolol: 1-5 mg/kg/day Sotalol: 0.5-2.5 mg/kg/day Amiodarone: 75-250 mg/m^2/day Propranolol: 1-3 mg/kg/day	Re-entry tachycardia: 4.5±5.2 Automatic tachycardia: 24.1±11.1	35 months	4	They found that flecainide and beta-blockers convert automatic or re-entry tachycardia to sinus rhythm in infants under one year old.
Wei et al.	2022	Prospective study and a literature review	108	9 (0-324)	70.8%	AVRT, AVNRT, undifferentiated re-entrant SVT	Flecainide: N/A Sotalol: N/A Amiodarone: 7.2-21.6 mg/day (for first medication) Propranolol: 1-1.5 mg/day (for first medication) Esmolol: 144-216 mg/day (for first medication) Digoxin: 0.025 mg/day (for first medication) Procainamide: 28.8 mg/day (only for second medication)	N/A	1 year	9	Comparing combination therapy to monotherapy, there was no statistically significant difference in the percentage of SVT control.
Bruder et al.	2022	Retrospective study	67	14 (0-254)	34 (51)	Focal atrial tachycardia, AVRT, AVNRT	Digoxin: 0.6-1.3 nmol/L Amiodarone: 10-15 mg/kg/day Propranolol: 3-5 mg/kg/day Flecainide: 3-8 mg/kg/day Propafenone: 150-600 mg/kg/day	N/A	23 months	0	Arrhythmia management is frequently achieved with a single drug, and most patients are arrhythmia-free after discontinuation.
Lim et al.	2022	Retrospective study	18	10.5 (7.25-19.8)	13 (72.2%)	N/A	Atenolol, amiodarone, flecainide, propranolol (The average dosage of drugs was not available)	362 days	N/A	0	Among patients, propranolol was the most frequently administered, followed by amiodarone. Only seven patients were able to be managed with monotherapy. Therefore, the appropriate combination of medications should be identified.
Aljohani et al.	2021	Retrospective study	74	6	47 (63.5)	AVRT, AVNRT	Flecainide, digoxin, sotalol, amiodarone, propranolol (The average dosage of drugs was not available)	6.7 months	15 months	0	Overall, they found that shortened treatment courses of 4-6 months for infants with SVT do not correlate with an increased risk of recurrence when compared to the conventional treatment durations of 6-12 months.

Kiskaddon et al.	2023	Retrospective study	31	16 (1-28)	21 (60)	N/A	Sotalol: 120 mg/m^2/day	N/A	N/A	2	Overall, this study indicated that for rhythm control in infants with SVT, a sotalol approach substantially greater than the manufacturer's dose guidelines is required.
Nicastro et al.	2020	Retrospective study	107	190	62	N/A	Propranolol: 2 to 5 mg/kg/day	N/A	1 year	2	In 70% of cases, propranolol reduced SVT recurrence.
Hill et al.	2019	Retrospective study	74	46	44 (59.4)	ORT, EAT, IART	Flecainide: 92 mg/m^2/day Amiodarone: 4.9 mg/kg/day	N/A	4.6 ± 2.9 years.	10	There was no statistically significant difference in the effectiveness of flecainide in comparison to amiodarone.
Epcacan	2019	Retrospective study	46	16.63 ± 7.61	27 (58.7)	WPW, PJRT, atrial flutter, multifocal atrial tachycardia	Adenosine, flecainide, propafenone, digoxin, esmolol, sotalol, amiodarone, propranolol (The average dosage of drugs was not available)	N/A	18.5 months	0	They discovered that greater doses of adenosine (300-500 μg/gr/kg) are particularly helpful in infants who are initially unresponsive to the normal dose of adenosine and are receiving acute therapy with esmolol and/or amiodarone continuous infusion.

IQR: Interquartile range, SVT: Supraventricular tachycardia, AVRT: Atrioventricular re-entry tachycardia, AVNRT: Atrioventricular nodal re-entry tachycardia, PJRT: Paroxysmal junctional re-entry tachycardia, WPW: Wolff-Parkinson-White, EAT: Ectopic atrial tachycardia, ORT: Orthodromic reciprocating tachycardia, IART: Intra-atrial re-entrant tachycardia, N/A: Not available.

was efficacious as monotherapy in 51.1% (23/45 cases) and in 44.4% (20/45 cases) when combined with digoxin, sotalol, or nadolol (total 95.5%). While 30% (3/10 cases) of individuals with automatic tachycardia found relief with a beta-blocker alone, the greatest outcomes were achieved when flecainide was added to the beta-blocker (90%). Overall, they discovered that in infants under one year with automatic or re-entry tachycardia, the combination of flecainide and beta-blockers was quite successful in maintaining sinus rhythm over the long term. However, flecainide had serious side effects in two people. Both adverse incidents were caused by accidental overdosing. Two more patients had only minor issues. As a result, they advised that due to the incidence of adverse events, this medication should be utilized with great caution at all times, and monitoring flecainide blood levels could be useful in this regard.

In 2022, Wei et al. [19] conducted a study on 108 infants with SVT for evaluating drug management. A total of 101 patients (93.5%) received antiarrhythmic therapy. The most common first-choice acute antiarrhythmic was propranolol (61.4%). Adequate SVT control was achieved in 56 of 80 monotherapy patients, including 45 of 62 patients on propranolol. Twelve (57.1%) of the 21 patients who underwent combination therapy had sufficient control. Comparing combination therapy to monotherapy, there was no statistically significant difference in the percentage of SVT control ($P < 0.07$). Also, there were no adverse effects observed among the participants.

In 2022, Bruder et al. [17] assessed the effectiveness of medication treatment for SVT in infants during the first year of life. Out of the 67 patients who underwent analysis, 48 demonstrated AVRT, 18 demonstrated focal atrial tachycardia and one presented with AVNRT. Fetal tachycardia was found in 27% of the cases. Beta-blockers were administered to 42 patients due to arrhythmia, propafenone to 20 patients, amiodarone to 20 patients, and digoxin to 5 patients. In 70% of patients, single-drug therapy was sufficient to obtain arrhythmia control; in 21%, dual therapy was required; and in 6%, triple therapy was indispensable. Because of the expansion of the QRS complex, propafenone was terminated in seven infants. After 12 months, 75% of survivors were tachycardia-free and no longer required preventive therapy. Patients who experienced fetal tachycardia were at a significantly increased risk of developing persistent tachycardia.

In 2022, Lim et al. [25] conducted a study on 18 infants with SVTs to evaluate the effectiveness of drug therapy. To prevent a recurrence of tachycardia, maintenance therapy involves the use of four medications: flecainide, atenolol, amiodarone, and propranolol. Among these, propranolol was the most frequently administered, followed by amiodarone. Only seven patients were able to be managed with monotherapy, and they all used propranolol alone. In contrast, at least two medications were necessary for the remaining patients. A total of four drugs are required for only one patient. The median time from the start of medication following diagnosis to the last tachycardia incident was 15.5 days, with a total medication duration of 362 days. Antiarrhythmic drugs had no adverse effects on any of the individuals.

In 2023, Kiskaddon et al. [26] evaluated the efficacy of sotalol for managing 31 infants with SVTs. The median dose at the beginning of treatment was 114.3 mg/m^2/day. For SVT management, 45.2% of patients needed a dosage increase. For rhythm control, a median dose of 120.7 mg/m^2/day was needed. Notably, the median suggested dose for patients according to the manufacturer nomogram would have been 51.3 mg/m^2/day, which is much lower than both the starting ($P < 0.001$) and final ($P < 0.001$) doses used in this investigation. On sotalol monotherapy, 7 (22.9%) individuals were uncontrolled in utilizing the dosage schedule. Two patients (6.5%) had hypotension, and one patient (3.3%) reported bradycardia that necessitated therapy termination. After initiating sotalol treatment, the mean change in baseline QTc was 6.8%. QTc was prolonged in twenty-seven (87.1%), unchanged in three (9.7%), and decreased in one (3.3%) case. Overall, this study indicated that for rhythm control in infants with SVT, a sotalol approach substantially greater than the manufacturer's dose guidelines is required.

In 2019, Hill et al. [27] compared oral flecainide versus amiodarone for SVT management in pediatrics. Seventy-four patients with a mean age of 46 days were included in this study. Flecainide and amiodarone was used in 47 and

27 cases, respectively. There was no statistically significant difference in the effectiveness of flecainide in comparison to amiodarone, as determined by comparing the rates of complete success (68% vs. 59%, P = 0.44) and partial or complete success (81% vs. 78%, respectively, P = 0.75). Also, patients who did not respond to amiodarone had promising results after switching to flecainide. Of patients using amiodarone and flecainide, minor adverse effects happened in 9% and 22% of cases, respectively.

In 2019, Epcacan [28] conducted a similar study to evaluate the medical management of neonatal SVT. Among 46 infants diagnosed with SVT, most of them had common SVT with a narrow QRS and a short RP (76%). In 84.4% of cases, SVT was terminated with adenosine. In 39.1% of patients, esmolol and/or amiodarone were used for acute therapy. In two patients, combined therapy of propafenone, propranolol, and digoxin was administered, and during follow-up, the treatment was shifted to a flecainide and amiodarone combination. In one patient, propafenone, amiodarone, and propranolol were combined, and later propafenone was changed to flecainide in the same combination. Although flecainide was normally introduced as the final option in combination therapies, they considered that, following good outcomes and no adverse effects, it may be administered as a second-line treatment along with amiodarone. Furthermore, they discovered that greater doses of adenosine (300-500 μg/gr/kg) are particularly helpful in infants who are initially unresponsive to the normal dose of adenosine and are receiving acute therapy with esmolol and/or amiodarone continuous infusion.

In 2021, Aljohani et al. [29] evaluated the duration and efficacy of drug therapy to reduce the recurrence of infant SVT. As an initial medication, propranolol was administered to 74.3% of infants. In 50% of patients, a second medicine, such as digoxin (24.3%) or flecainide (51.4%), was required in addition to propranolol. SVT recurrence occurred in 13.2%, 16.7%, and 33.3% of patients who received antiarrhythmic drugs for less than 6 months, 6 to 12 months, and more than 12 months, respectively. Overall, they found that shortened treatment courses of 4-6 months for infants with SVT do not correlate with an increased risk of recurrence when compared to the conventional treatment durations of 6-12 months.

In 2020, Nicastro et al. [30] evaluated the use of propranolol to manage infant SVT. One hundred and seven infants were involved in this investigation. The daily dose of propranolol ranged from 2 to 5 mg/kg. In 70% of cases, propranolol reduced SVT recurrence. However, due to serious side effects, medication was stopped in two patients.

According to the present research, there is no first- or second-line treatment for SVT in infants because a beneficial medicine may be ineffective in other individuals; all options should be evaluated during the treatment procedure. Propranolol was successful in the majority of infants and can be recommended as a first-line treatment for infant SVT in emergencies. However, a combination of medications is frequently more effective and has fewer complications.

In this review, we did not exclude studies involving infants with congenital heart defects. Also, the duration of therapy was not reported clearly in most articles that we evaluated.

Conclusion

This research concludes that the therapy for infant SVT is mostly based on the patient's history and the likely adverse effects of certain medicines that need to be avoided. Propranolol was successful in the majority of infants and can be recommended as a first-line treatment for infant SVT in emergencies. However, a combination of medications is frequently more effective and has fewer complications.

Disclosure of conflict of interest

None.

Address correspondence to: Azad Mojahedi, Department of Internal Medicine, Stony Brook University Hospital, Stony Brook, New York, The United States. Tel: 818-519-1953; +98-9112774184; Fax: +98-3137265007; E-mail: Azad.mojahedi@stonybrookmedicine.edu

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