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The Drugs Used in the Treatment of Supraventricular Tachycardia in Pediatrics: A Systematic Review and Meta-Analysis

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SOUHRN

Kontext: Termínem supraventrikulární tachykardie (SVT) se označuje abnormálně rychlý srdeční rytmus v důsledku poruchy elektrické aktivity v horních segmentech srdce. Akutní léčba dětských pacientů se SVT může představovat náročný úkol, protože přesný mechanismus vzniku tachykardie často není znám. Volba léčebné strategie závisí na projevech a na klinickém stavu pacienta.
Metodologie: Byla provedena systematická rešerše literatury s cílem vyhledat a vybrat zprávy a články o originálním výzkumu na téma farmakologické léčby SVT u dětí a kojenců bez strukturálního onemocnění srdce (všichni od první hodiny života až do 17 let věku) v souladu s doporučenými postupy PRISMA. Údaje byly analyzovány s použitím softwaru Review Manager version 5.4. Statistická významnost rozdílů se vyjadřovala hodnotou *p* a heterogenita/homogenita analyzovaných studií indexem I^2.
Výsledky: Do přehledu bylo zařazeno 26 studií z celkem původně vybraných 65 studií hodnocených z hlediska vhodnosti a splnění zadaných kritérií. Údaje se týkaly 8 103 pacientů se SVT ze 13 zemí, léčených různými antiarytmiky včetně adenosinu a dexmedetomidinu v akutních případech, a podáváním amiodaronu, beta-blokátorů, flekainidu, digoxinu a ivabradinu pacientům sloužícím jako chronické kontroly. Byl nalezen statisticky významný rozdíl mezi pacienty užívajícími uvedená léčiva a pacienty, kteří na léčivo reagovali ($p < 0{,}005$ a $I^2 = 72$ %).
Závěr: V pediatrii neexistuje léčba SVT první nebo druhé linie a účinnost léčiv se může mezi jednotlivými pacienty značně lišit; pro léčbu je nutno zvážit všechny možnosti. Na rozdíl od podávání jednotlivých léčiv jsou jejich kombinace účinnější při menším počtu nežádoucích účinků. Podle tohoto přehledu závisí léčba SVT u kojenců na anamnéze pacienta; přitom je třeba mít na paměti možné nežádoucí účinky některých léčiv.

ABSTRACT

Background: Supraventricular tachycardia (SVT) is an abnormally rapid heart rhythm that results from improper electrical activity in the upper part of the heart. Acute management of children presenting with SVT may be a challenge, as the exact tachycardia mechanism is often unknown. The strategy for treatment depends on the presentation and clinical status of the patient.
Methodology: A systematic literature review was conducted to identify and select original research reports on supraventricular tachycardia management drugs in children and infants with no structural heart disease (all children from 1 hour to 17 years of age) in accordance with the PRISMA guidelines. Data were analyzed with Review manager version 5.4. *P*-value and I^2 were used to test the significance difference.
Results: 26 studies out of 65 total studies assessed for eligibility were included in the review by fulfilling the inclusion criteria. There were 8103 patients from 13 countries with SVT who were treated with different antiarrhythmic drugs including (Adenosine, Dexmedetomidine) as acute management and (Amiodarone, Beta-Blockers, Flecainide, Digoxin and Ivabradine) as chronic control. There was a significant difference between the patients who took the drugs and the patients who responded to the drugs, with *P*-value <0.005 and $I^2 = 72\%$.

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Conclusion: There is not a first line treatment or second line treatment for SVT in pediatrics, and drug effectiveness can vary greatly between patients; all choices should be considered during the treatment protocol. The combination of drugs, as opposed to a single drug, is more efficient with less side effects in these patients. According to this review, the management of SVT in infants is highly dependent on the history of the patient and the probable side effects of some treatments that must be avoided.

Introduction

Supraventricular tachycardia (SVT) is an abnormally rapid heart rhythm that results from improper electrical activity in the upper part of the heart.[1]

It originates above the ventricles, and frequently (but not always) presents with a narrow QRS complex; atrial flutter and atrial fibrillation are conventionally omitted.[2]

Other names such as paroxysmal (start and stop without warning) atrial tachycardia (PAT) and paroxysmal supraventricular tachycardia (PSVT) are sometimes used for SVT. Wolff–Parkinson–White Syndrome (WPW) is a variant of SVT, and is the most common form of SVT in young people.[1,2]

SVT is almost never life-threatening and the outcomes of treatment are outstanding. SVT causes irregular heart pounding symptoms, which can lead to chest pain, shortness of breath, lightheadedness, and/or fainting. The episodes can be related to exercise. Even though the SVT configuration is often present at birth, symptoms can begin at any time.[3] A 50% risk then exists that the SVT will recur as an older child.[4]

SVT may be diagnosed in infants as a result of symptoms of congestive heart failure. Babies can tolerate a very fast heart rate for many hours without showing any symptoms. If the episode lasts for more than 24–36 hours, the heart muscle tires slowly and pumps with less and less force.[5]

During this time, symptoms include inadequate eating, excessive sleepiness, irritability, diarrhea, fast breathing, and/or light skin color.[5]

Acute management of the child presenting with SVT may be a challenge, as the exact tachycardia mechanism is often unknown. The strategy for the treatment depends on the presentation and clinical status of the patient (hemodynamically stable or unstable), which is why SVT is very important and must be addressed.[6]

For most babies, the natural history of SVT requires resolution of the tachycardia by one year of age. Pharmacological treatment is usually used to eliminate tachycardia before spontaneous resolution occurs, but often conventional first-line therapy like digoxin or propranolol does not lead to SVT control.[7]

Drugs that are commonly used for SVT in children are digoxin, propranolol, flecainide, and amiodarone. Although different types of SVT may vary in pathophysiology, we use the same medications.

In this review, the aim is to compare the efficacy and the frequency of drug use in the management of SVT to find out the most beneficial and the safest drug for treatment.

Methodology

Selection of studies

A systematic literature review was conducted to identify and select original research reports on supraventricular tachycardia management drugs in children and infants (all children from hour to 17 years of age) in accordance with the PRISMA guidelines.[8]

The online databases Google Scholar, PubMed, Medline, and Cochrane were searched from January 2000 to June 2020. Keywords used in the search included (Supraventricular tachycardia in children OR Supraventricular tachycardia in infants OR Supraventricular tachycardia in pediatric) AND (Treatment of supraventricular tachycardia in infant / Children / Pediatric OR Management of Supraventricular tachycardia in infant / Children / Pediatric). The references of each study were manually checked for additional relating studies. Only peer-reviewed journal articles that documented initial investigations, case reports, case series, and clinical trials of the drugs used to treat SVT in pediatric patients with no structural heart disease aged from hour to 17 years were included. We excluded the following: 1) studies involving pediatric patients with structural heart disease; 2) studies having inadequate or inaccurate data for extraction; 3) reviews, book chapters, theses, editorials, letters, and conference papers; 4) non-English research; 5) animal or *in vitro* studies; 6) non-clinical studies, systematic reviews of the literature, meta-analyses, and research for which only an abstract is available. We did not deviate from the defined inclusion criteria and thoroughly evaluated related research, including existing literature reviews, to be sure that bias was minimized within the systematic review

An analysis of the funnel plot was carried out to determine the possibility of bias in the publication.

Data extraction

Mean, standard deviation, and sample size were extracted for each variable. The authors were kindly contacted to provide numbers if the data were presented in statistics and not in specific values. We excluded any studies without an electrocardiogram (ECG). The drugs used in the treatment were extracted with their details of dose, onset of action, duration, and efficacy.

Analysis

A meta-analysis of comparable data was performed using version 5.4 of the Review Manager software.

Using the I^2 statistics, statistical heterogeneity among studies was assessed. Pronounced heterogeneity was seen with a p-value ≤ 0.05 and an I^2-value $\geq 50\%$. A p-value ≥ 0.05 and $I^2 \leq 50\%$ indicated no obvious heterogeneity be-

tween the studies, and the meta-analysis was based on a fixed effect model.

Generic Inverse Variance data are described as weighted mean differences, and odd ratios (ORs) for dichotomy were determined (95% for confidence interval). Egger's test was conducted to determine the possibility of a bias in publishing.

Furthermore, a sensitivity analysis was conducted to determine the reliability of the findings when the study included low-quality and extremely heterogeneous studies.

Results

The database search retrieved 490 results as seen in Figure 1: 475 from Google Scholar, PubMed, Medline, and Cochrane, and 15 from additional records found via other sources. Duplicates were removed from the 490 records. Following the removal of duplicates, there were 263 results to screen. The studies were checked for eligibility in the title and abstract, leaving 65 records to be evaluated. Thirty-nine records, however, were excluded for the following reasons: 1) non-English studies; 2) only abstracts and reviews; 3) incomplete data or results. Twenty-six publications were chosen for data extraction.

Table 1 shows the characteristics of individual studies

The ages of the patients in Table 1 are shown in mean for some studies and median for others. Two studies did not mention the age data.

Some of the studies depended on gestation age, so we showed them as weeks (w).

For the years of the studies, some studies take data for several years behind and analyze them, so those are shown as a range. Studies that depended on the data of a single year are shown as a single value.

Table 2 shows the drugs used and studies results.

Figure 2 shows the risk of biases among the studies, organized as high risk, low risk, and unclear risk.

Table 3 shows the studies that recorded side effects during drug administration and the number of patients who experienced them.

Only the studies classified in Table 3 recorded significant adverse effects of the administered drugs, while the other studies did not mention any side effect.

Figure 3 is a forest plot of the dichotomy variables testing the efficacy of the drugs used in each study depending on the number of patients who received these drugs with the number of patients who successfully responded to the drugs.

A p-value ≥ 0.05 and $I^2 \leq 50\%$ indicated no obvious heterogeneity between the studies, and the meta-analysis was based on a fixed effect model.

There was a significant difference between the patients who took the drugs and the patients who responded to the drugs, with p-value <0.005 and $I^2 = 72\%$.

A comparison between the number of patients who received the drugs and the number of patients who experienced adverse effects is clarified in Figures 4 and 5 as a forest plot and a funnel plot using heterogeneity, with $I^2 = 94\%$ and p-value <0.005.

Table 1 – The characteristics of the included studies

The study	Drugs	Year	Country	Study design	Patients No.	Mean age	Ref.
Qureshi	Adenosine	2008–2012	Pakistan	Experimental	85	27.9 m	9
Diaz-Parra	Adenosine	2014	Spain	Retrospective	39	3.1 y	11
Dixon	Adenosine	2005	UK	Retrospective	23	–	33
Lewis	Adenosine	2003–2012	USA	Retrospective cohort	174	7.4 y	29
Chu	Adenosine, amiodarone, esmolol, procainamide, beta-blocker, digoxin, flecainide	2015	USA	Retrospective	2481	34.38 w	18
Epcacan	Adenosine, amiodarone, esmolol, procainamide, beta-blocker, digoxin, flecainide	2014–2018	Turkey	Retrospective	46	38.04 w	21
Sadoh	Adenosine, beta-blockers, digoxin	2018	Nigeria	Descriptive	29	4 m	14
Burri	Amiodarone	2003	Switzerland	Retrospective	23	8 d	17
Yildirim	Amiodarone	2005	Turkey	Case report	1	7 hours	10
Dilber	Amiodarone, digoxin	2005–2007	Turkey	Retrospective	9	15 d	22
Chang	Amiodarone, procainamide	2004–2006	USA	Retrospective	208	34 d	19
Etheridge	Amiodarone, propranolol	2001	USA	Retrospective	50	1 m	23
Hultin	Dexmedetomidine	2018	Sweden	Case report	2	1.5 y	28
Sanatani	Digoxin and propranolol	2006–2010	Canada and USA	Randomized, double-blind, multicenter	72	11.75 d	20
Venugopalan	Digoxin, amiodarone, adenosine	2000	Oman	Case reports	3	6.16 y	32

Continue

Table 1 – The characteristics of the included studies

The study	Drugs	Year	Country	Study design	Patients No.	Mean age	Ref.
Ferlini	Flecainide	2004–2006	Italy	Retrospective	20	11.5 d	24
Hill	Flecainide, amiodarone	2006–2015	USA	Retrospective	74	46 d	27
Price	Flecainide, sotalol	2002	USA	Retrospective	10	24 d	12
Taduri	Ivabradine	2019	India	Case report	1	15 d	13
von Alvensleben	Nadolol	2017	USA	Retrospective	20	18 d	34
Barton	Propranolol	2015	USA	Retrospective	287	29 d	15
Nicastro	Propranolol	2001–2018	Argentina	Observation	107	190 d	25
Bolin	Propranolol, digoxin	2004–2015	USA	Retrospective	2657	37 w	16
Hornik	Propranolol, digoxin	1998–2012	USA	Retrospective cohort	457	7–9 d	31
Moffett	Propranolol, digoxin	2015	USA	Retrospective cohort	374	33 d	30
Guerrier	Propranolol, digoxin, amiodarone	2003–2013	USA	Retrospective	851	–	26

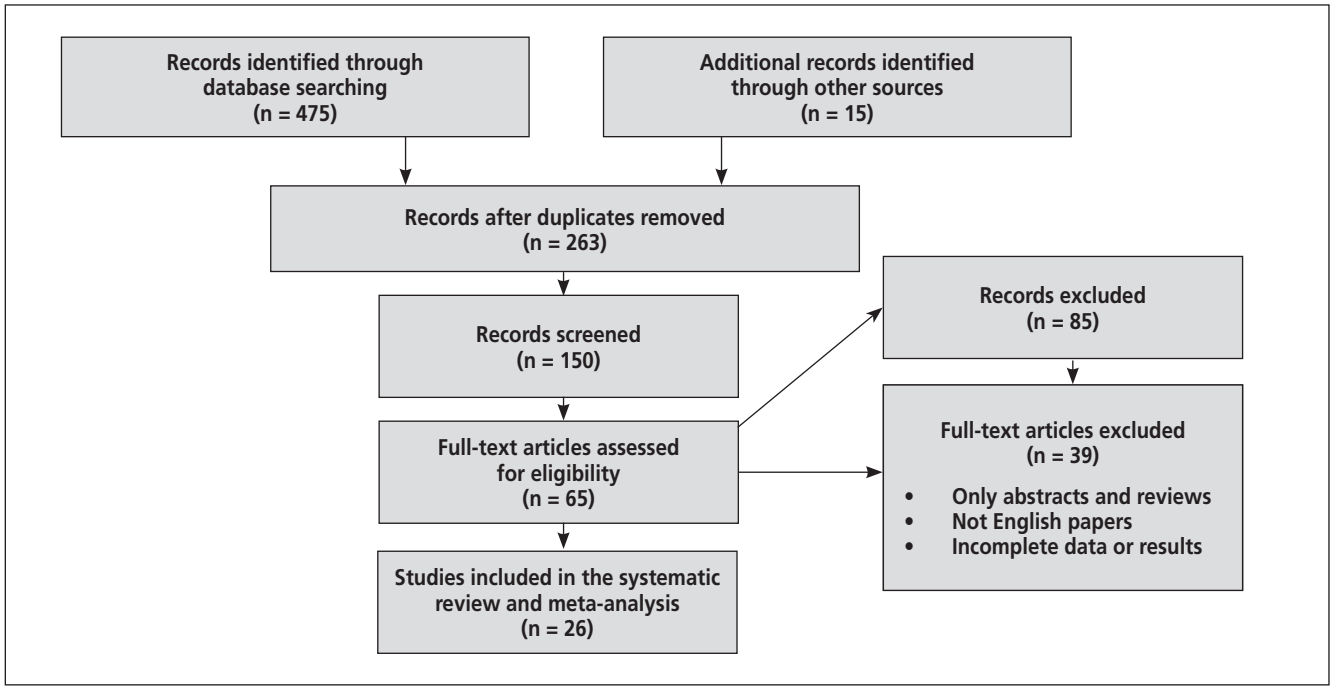

Fig. 1 – Flow chart of the study selection process.

Table 2 – The data of the drugs used and their outcomes among studies

	The drug	Doses	Administration	Outcomes	Ref.
Acute management of SVT	Adenosine	100, 200, 300	Rapid boluses	Mean effective dose was 185.3+81.0 μg/kg with median effective dose of 200 μg/kg (range 75–300 μg/kg)	9
	Adenosine	112, 118, 249, 300 μg/kg	Rapid boluses	The administration of adenosine in childhood is effective in the cessation of the SVT in 70% to 85% of cases	11
	Dexmedetomidine	4 μg/kg	Intranasal	Spontaneous conversions of SVT to sinus rhythm in children	28
	Adenosine	0.05–0.25 mg/kg 0.1–0.48 mg/kg	Infusion	Overall, adenosine was effective for the successful termination of SVT: 79% of episodes converted to sinus rhythm after 1 or 2 doses of adenosine	29
	Adenosine	115 μg/kg	Infusion	The minimum dose to be effective should be no less than 100 μg/kg in children and 150 or 200 μg/kg in infancy	33
	Adenosine, beta--blockers, digoxin	–	Rapid boluses	Of the 29 children 18 (62.1%) survived and were discharged home while 11 (37.9%) died	14

Continue

Table 2 – The data of the drugs used and their outcomes among studies

	The drug	Doses	Administration	Outcomes	Ref.
Chronic control of SVT	Amiodarone	10 mg/kg administered in 1 hour	Infusion	After 30 minutes, the patient converted to normal sinus rhythm with a heart rate of 130 beats/min	10
	Flecainide + sotalol	100 mg/m^2/day + 175 mg/m^2/day (twice daily)	Infusion	Generally, normal sinus rhythm was observed by telemetry within 2 to 5 days, and efficacy was documented by Holter within 3 days to 90 days (median: 12 days)	12
	Ivabradine	0.05 mg/kg/day	Infusion	It ameliorated the atrial tachycardia and the heart rate was normalized	13
	Propranolol	3.6±1.0 mg/kg/day	–	Propranolol was successful in controlling arrhythmias throughout the inpatient stay in 67.3% (n = 193) of patients overall	15
	Propranolol, digoxin	–	–	After matching, there was 1.7% mortality in the propranolol group versus 6.1% mortality in the digoxin group for all patients	16
	Amiodarone	12.2±4.6 µg/kg	Intravenous	Intravenous amiodarone is a safe and effective therapy for life-threatening incessant tachycardia in infants	17
	Amiodarone, procainamide	5 µg/kg/min, 20 µg/kg/min	Continuous infusion	Procainamide achieved greater success compared with amiodarone in the management of recurrent SVT without statistically significant differences in adverse event frequency	19
	Digoxin, propranolol	–	–	There was no difference in SVT recurrence in infants treated with digoxin versus propranolol	20
	Adenosine, amiodarone, flecainide	100–500 µ/kg	Continuous infusion	Higher doses of adenosine (300–500 µg/kg) is very effective. Amiodarone alone and in combination with flecainide seems safe and effective, too.	21
	Amiodarone, digoxin	2.5–30 µg/kg/min	Intravenous	Intravenous amiodarone alone or in combination with digoxin was found to be safe and effective therapy in controlling refractory and life-threatening SVT in neonates and small infants	22
	Amiodarone, propranolol	14±5 mg/kg/day in 2 doses	Intravenous	Amiodarone is an effective and safe therapy for tachycardia control in infancy	23
	Flecainide	1 mg/kg 2 mg/kg/day	Intravenous Orally	Flecainide is well tolerated and effective as first-line treatment for paroxysmal SVT in newborns without structural heart disease	24
	Propranolol	3±0.5 mg/kg/day	Orally	Propranolol prevented SVT recurrence in 70% of patients	25
	Propranolol, digoxin, amiodarone	–	–	No difference in patient outcomes with different drugs	26
	Flecainide, amiodarone	92 mg/m^2/day, 4.9 mg/kg/day	Orally	Oral flecainide and amiodarone achieved meaningful arrhythmia control in 81% and 78% of pediatric patients with recurrent SVT, respectively. Those who failed amiodarone had encouraging outcomes when changed to flecainide.	27
	Propranolol, digoxin	4 mg/kg/day, 10 µg/kg/day, divided every 12 h	Infusion	Digoxin or propranolol may have similar efficacy in the inpatient treatment of infant SVT. The effects of medication dosing strategies and patient pathophysiology may need to be considered for antiarrhythmic selection to attain best possible patient outcomes.	30
	Propranolol, digoxin	≥3 mg/kg/day, 4–12 µg/kg/day	Infusion	Digoxin was associated with fewer episodes of SVT recurrence but more frequent hypotension in hospitalized infants relative to propranolol	31
	Amiodarone, adenosine	0.1 mg/kg, 3 doses	Intravenous	Adenosine was effective to suppress the SVT as well as amiodarone	32
	Nadolol	1 mg/kg/day	Orally	Nadolol monotherapy can be used successfully in the treatment of SVT in infants and young children with minimal side effects	34

Table 3 – The side effects' characteristics shown in the studies

The drug	Ref.	The side effect	No. of patients
Amiodarone	10	Hyperglycemia, pulmonary fibrosis, thyroid dysfunction, and hepatic failure	1
Intravenous amiodarone	17	Electrophysiological side effects necessitating dose reduction comprised of sinus bradycardia in two patients. Hypotension in one patient resolved after dose diminution. Neurological side effects consisted of choreatic movements in one infant, which resolved over time. Amiodarone administration was stopped in one patient with elevated liver enzymes.	5
Amiodarone, procainamide	19	Hypotension, bradycardia, QRS prolongation, and QT prolongation	50
Digoxin, beta-blockers, amiodarone, flecainide, sotalol	18	Hypotension, hyperkalemia, hypoglycemia, elevated liver enzymes, and bradycardia	669
Amiodarone	23	There were no side effects necessitating drug withdrawal. Acute hypotension occurred in 2 patients during intravenous amiodarone infusion and resolved with volume administration.	2
Propranolol	25	Sensory deficit and vomiting, and symptomatic hypoglycemia (blood glucose below 50 mg/dL) was detected in the context of concurrent viral infections	2
Flecainide and amiodarone	27	BBB, bradycardia, ventricular dysfunction, inadvertent overdose, hypothyroidism, and leukopenia	10
Digoxin and propranolol	31	Hypotension was more frequent during exposure to digoxin versus propranolol	457

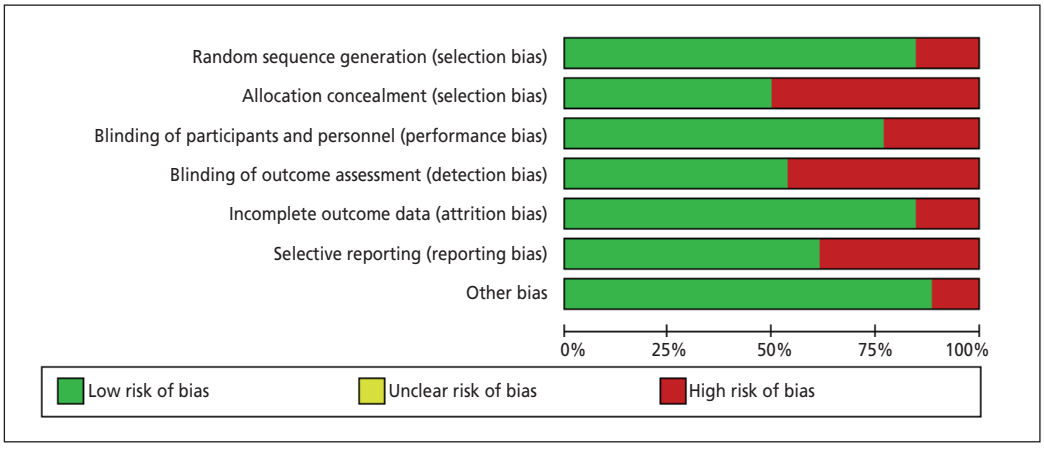

Fig. 2 – The risk of biases among studies

Discussion

There were 8103 pediatric patients from 13 countries with SVT who were treated with different antiarrhythmic drugs including adenosine and dexmedetomidine for acute management and amiodarone, beta-blockers, flecainide, digoxin, and ivabradine for chronic control.

SVT in pediatrics can be fatal and acute management is very important in order to restore normal sinus rhythm, so selecting the most appropriate drug for the case is essential and time-saving. Proper drug selection should also reduce the adverse effects that can be produced by the drugs in certain patients.

The 26 studies that were included in this review depended on data from the registration offices of the hospitals and healthcare centers, as well as observational data and randomized clinical trials.

Some centers select a first line and second line treatment for SVT in pediatrics, but according to this review and based on the data extracted from the studies, no appropriate first- or second-line treatment was found; for example, if we take adenosine, which is commonly used along with digoxin, as a first line treatment for SVT in pediatrics, it may be tolerated by some infants while also being useless in many patients.

Some centers used a combination of two or more drugs to control SVT in pediatrics.

The dosage is a very important factor in the efficacy of the drugs, and this was shown in almost all the studies included. Increasing the dose can bring about more problems to the child, including adverse effects, toxicity, and heart problems such as bradycardia.

Adverse effects were observed in 8 studies (Table 3) and they were most commonly associated with amiodarone.

Using the statistical testing results, we found that there was a strong association between the number of patients who received the drugs and the number of patients who experienced adverse effects. There was a significant difference

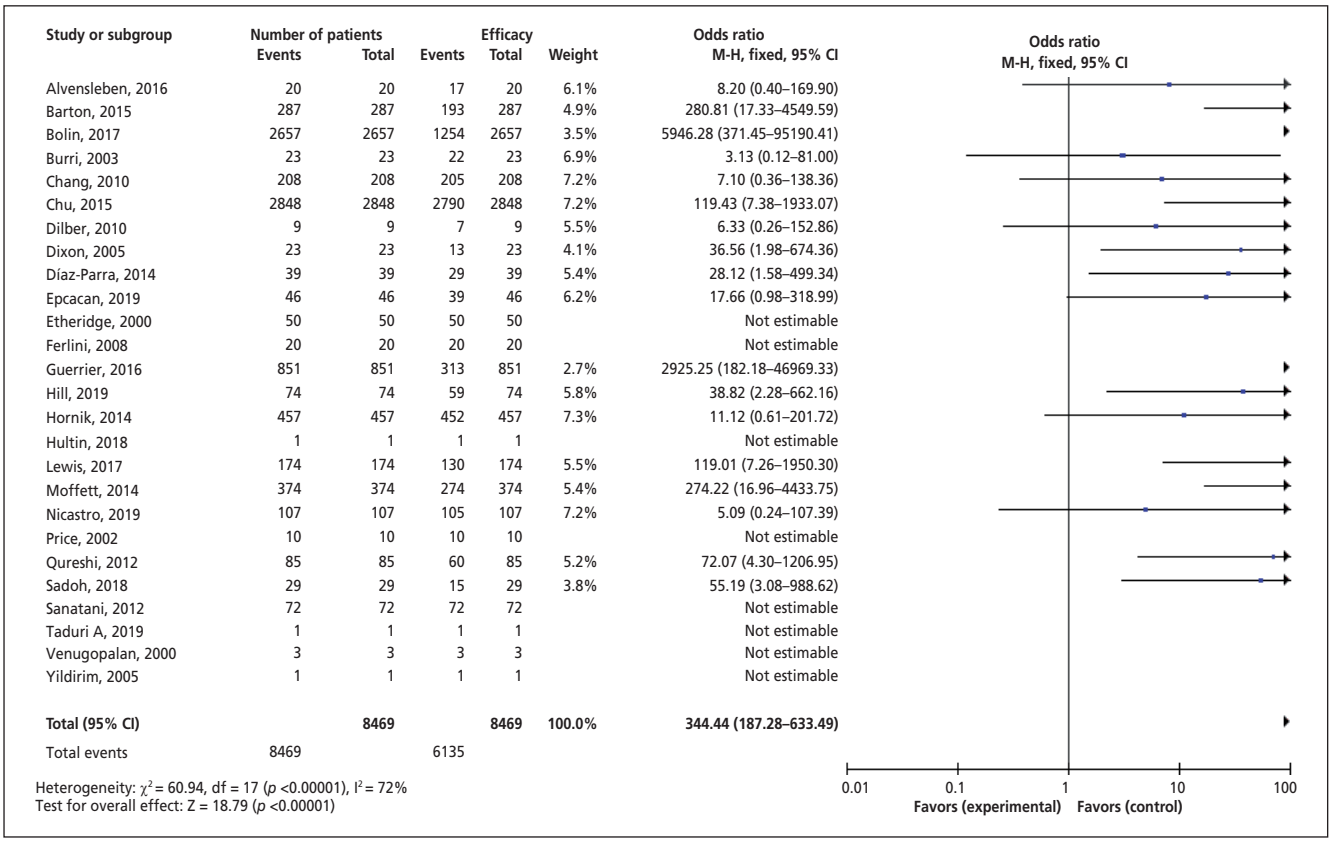

Fig. 3 – Forest plot of the dichotomy variables.

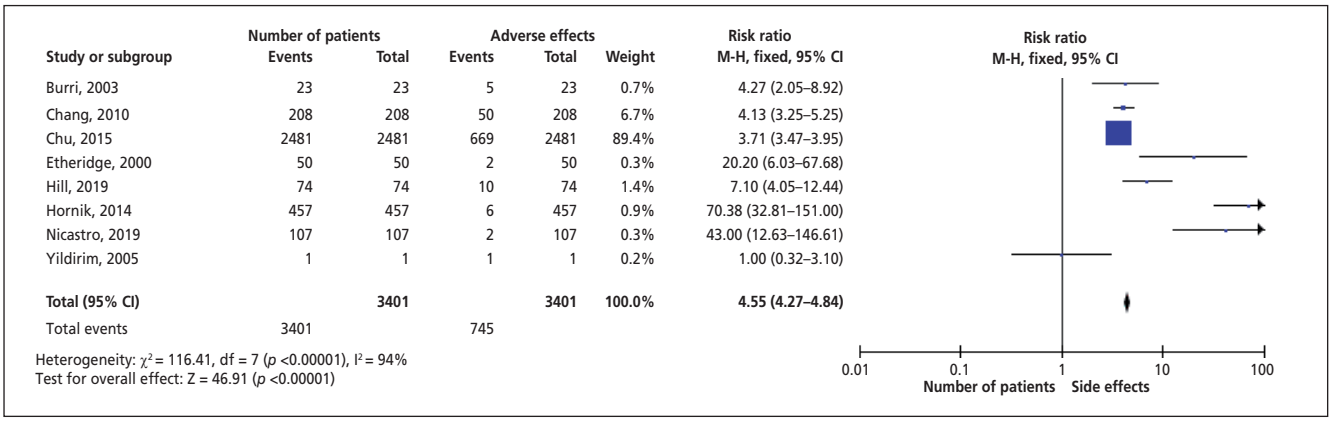

Fig. 4 – Forest plot of comparison between the number of patients who received the drugs and the number of patients who experienced side effects.

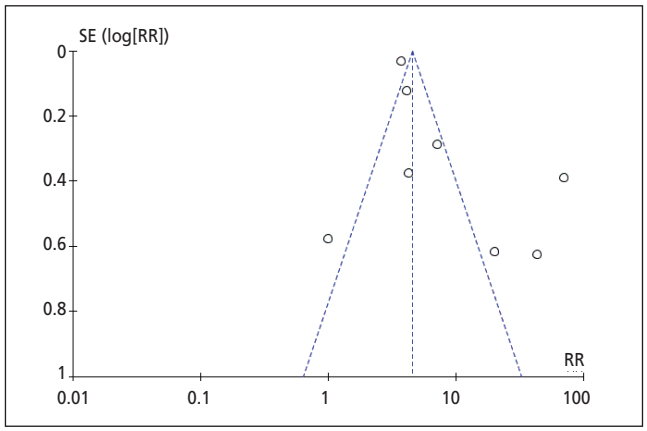

Fig. 5 – Funnel plot of the same comparison in Figure 4.

between the number of patients who received the drugs and the patients who recovered from SVT successfully.

The route of administration has no specific or effective role in increasing the drugs' efficacy or effectiveness, and the dosage was the only factor that controlled the efficacy among the patients (the combination therapy also played a role, but can be considered a line of treatment rather than a factor).

Flecainide and digoxin were effective in many cases, and can be recognized as a first line treatment in emergencies for pediatric patients.

Two unpopular drugs that produced an effective role in treating SVT in pediatrics included ivabradine and dexmedetomidine.[35,36]

Conclusion

SVT is a common manifestation in pediatrics, and should be treated with less adverse effects. This review presents the most common drugs used in the treatment of SVT in children from 2000 to 2020, including their efficacy and any associated adverse effects.

There is not a first-line treatment or second-line treatment of SVT in pediatrics, since an effective drug can be ineffective in othes patients; all choices should be considered during the treatment protocol, keeping in mind that a combination of drugs is often more efficient and with less side effects.

According to this review, the management of SVT in infants is highly dependent on the history of the patient and the probable side effects of some treatments that must be avoided.

Conflict of interest

The authors declare that they have no conflicts of interest.

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