Ther Adv Cardiovasc Dis

2015, Vol. 9(1) 4–9

DOI: 10.1177/1753944714553425

Oral verapamil in paroxysmal supraventricular tachycardia recurrence control: a randomized clinical trial

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Abstract

Background: Adenosine is the first-line medication in patients with paroxysmal supraventricular tachycardia. Because it is cleared so rapidly from the circulation, recurrence of paroxysmal supraventricular tachycardia after initial successful conversion may occur.

Objective: This study was conducted to evaluate the role of oral verapamil administration to control early recurrences of paroxysmal supraventricular tachycardia after adenosine infusion.

Methods: Patients with acute paroxysmal supraventricular tachycardia and no contraindications for adenosine or verapamil treatment were included in study. All patients received an adenosine protocol (6 mg rapid bolus intravenous injection followed by two repeated doses of 12 mg if necessary). Patients in the adenosine-only group did not received any other medications but patients in the adenosine/verapamil group received 40 mg verapamil orally immediately after converting the rhythm to sinus rhythm. All patients were followed up for 6 h in the acute care area of the emergency department under continuous cardiac monitoring.

Results: A total of 113 patients were assessed for eligibility and 92 patients were randomized into two groups (adenosine only *versus* adenosine/verapamil). There was no statistically significant difference in paroxysmal supraventricular tachycardia recurrence rate between the two groups in the first 30 min after treatment. Recurrence rate was statistically significantly lower in the adenosine/verapamil group than in the adenosine-only group between 30 and 120 min after treatment and thereafter. Two patients in the adenosine-only group experienced flushing and one patient in the adenosine/verapamil group experienced decreased systolic blood pressure.

Conclusion: Oral verapamil can decrease paroxysmal supraventricular tachycardia recurrence after successful control with intravenous adenosine.

Keywords: early recurrence control, oral verapamil, paroxysmal supraventricular tachycardia

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Introduction

Paroxysmal supraventricular tachycardia (PSVT) is a common rhythm disorder (seen in 2.5 per 1000 adults in the general population) [Ferguson and DiMarco, 2003]. It is typically caused by atrioventricular (AV) nodal reentry pathway and usually presents with distinct clinical presentations like sudden onset palpitations, anxiety, dizziness, shortness of breath, feeling faint and chest tightness. PSVT is usually a well tolerated self-limited condition which can easily be controlled by rest, vagal maneuvers and alleviating the precipitating stimulus. Antiarrhythmic drugs and cardioversion may rarely be needed [Kesh Hebbar and Hueston, 2002; Chan and Yuen, 2006].

Adenosine, an endogenous purine nucleoside, is an ultra-short-acting agent with a half life of 1–6 s. It interrupts the AV nodal reentry pathway and is used as first-line medication in control of PSVT

[Nolan *et al.* 2005]. Adenosine is cleared so rapidly from circulation (mainly by erythrocyte and vascular endothelial cell uptake) and PSVT may recur after initial successful conversion by adenosine [DiMarco, 2000]. Thus any complementary treatment which can reduce the rate of recurrence in successfully controlled PSVT cases is of interest.

Verapamil is a calcium channel blocker which inhibits calcium ion influx in direct proportion to its concentration in plasma. It has a bioavailability of 20–35% and plasma half life of 3–6 h, reaches its peak plasma level in 1–2 h, has no or few active metabolites and is eliminated by extra-renal routes. Verapamil can decrease the rate of sinus node discharges and slow down AV node conduction while maintaining the normal function of His-Purkinje fibers and ventricular myocardial cells, thus it is used to control atrial arrhythmia [McAllister *et al.* 1983; Burkart, 1992; McTavish, 1989].

This prospective randomized clinical trial was conducted to evaluate the efficacy of oral verapamil in decreasing the early recurrence rate of PSVT after successful control with intravenous adenosine in the emergency department.

Materials and methods

Study design and setting

This randomized clinical trial with convenient recruitment of patients during October 2010–August 2011 was conducted in a tertiary teaching hospital with a total annual census of 45,000 adult patients. The study was approved by the institutional ethics committee. Informed written consent was obtained from all patients and the trial was registered [ClinicalTrials.gov identifier: NCT01655316].

Participants

We included patients aged at least 18 years who were admitted to the emergency department with suspected PSVT [based on their rapid onset of symptoms and electrocardiogram (ECG) evidence of regular narrow complex tachycardia] who had not received any antiarrhythmic drugs before emergency department presentation and whose condition failed to respond to vagal maneuvers.

We excluded patients with hemodynamic instability (chest pain, decreased level of consciousness, hypotension or pulmonary edema due to congestive heart failure); known cases ofWolf–Parkinson–White syndrome (WPW) or structural heart disease; patients with known ischemic heart disease; patients with known allergy to adenosine or verapamil; patients with a contraindication to verapamil or adenosine (any evidence of severe heart failure, sick sinus syndrome, second- or third-degree AV block, WPW, history of asthma, heart transplantation, hypersensitivity to adenosine or verapamil).

Intervention

Patients with PSVT were triaged to the cardiopulmonary resuscitation room. They first underwent vagal maneuvers under cardiac monitoring. If the maneuvers were unsuccessful patients were included in our study.

All patients received 6 mg adenosine as a rapid bolus intravenous injection by the peripheral route followed by a rapid saline flush. If the first dose did not eliminate the PSVT within 1–2 min, 12 mg adenosine was administered intravenously again and then this 12 mg dose was repeated for a second time if required.

When the PSVT was controlled and the rhythm converted to sinus rhythm, patients were randomly allocated to the adenosine-only or the adenosine/verapamil group. We used computer-generated randomization blocks of four to make random allocation. Patients whose rhythm did not convert to sinus rhythm with adenosine were excluded from the study and other antiarrhythmic drugs were used.

Patients in the adenosine-only group did not received any other medications but patients in the adenosine/verapamil group received 40 mg verapamil orally immediately after the rhythm was converted to sinus rhythm.

All patients were followed up for 6 h in the acute care area of the emergency department under continuous cardiac monitoring. If the rhythm on the monitor changed, an ECG tracing was taken immediately and if the new ECG showed the recurrence of PSVT, the patient was treated accordingly.

Any evidence of verapamil or adenosine side effects (including excessive bradycardia, hypotension, nausea, vomiting, abdominal pain, headache,

dizziness, itching, trouble breathing, chest pain and flushing) was documented.

Measurements

Any evidence of rhythm disturbance was detected on continuous cardiac monitoring and was verified by immediate ECG tracing. Serial blood pressure control was done every 5–10 min by noninvasive blood pressure monitoring. Baseline vital signs and ECG findings were recorded before intervention and then 30 and 120 min after rhythm control with adenosine and verapamil intake. Early adverse effects of verapamil, including respiratory difficulties, circulatory compromise (more than 20 mmHg decrease in systolic blood pressure), dizziness, nausea and vomiting, itching, headache and hypersensitivity reactions were immediately recorded.

The primary outcome measure was the rate of maintaining sinus rhythm within 2 h after successful cardioversion and the secondary outcome was the occurrence of adverse effects of drugs.

Data analysis

Descriptive data are presented as minimum, maximum and mean (with standard deviation). We used Student's t test or the χ^2 test to compare means. All data analyses were performed with SPSS version 16 (SPSS, Inc., Chicago, IL, USA).

Results

Basic characteristics of study patients

There was no statistically significant difference in demographic characteristics and comorbid conditions between the two groups. There was also no statistically significant differences in baseline vital signs of patients including systolic and diastolic blood pressure, heart rate, respiratory rate and oxygen saturation between the two groups (Table 1). The flow of study subjects is illustrated as the CONSORT diagram (Figure 1).

Main results

In the first 30 min after treatment, PSVT recurred in 4 (8%) patients in the adenosine-only group and in 10 (21%) patients in the adenosine/verapamil group. There was no statistically significant difference in PSVT recurrence rate between the two groups in the first 30 min after treatment ($p = 0.078$).

Between 30 and 120 min after adenosine therapy, PSVT recurred in 21 (45%) patients in the adenosine-only group and in 13 (28%) patients in the adenosine/verapamil group. The recurrence rate was statistically significant lower in the adenosine/verapamil group than in the adenosine-only group ($p = 0.042$) between 30 and 120 min after treatment. In the rest of the follow-up period no further recurrence was seen in the two groups.

Complications

Two patients in the adenosine-only group experienced flushing and one patient in the adenosine/verapamil group experienced decreased systolic blood pressure.

Discussion

Maintaining the sinus rhythm in patients after successful rhythm conversion is an ideal goal in any acute cardiac care setting. PSVTs are successfully converted to sinus rhythm in emergency departments by applying vagal maneuvers, alleviating the precipitating factor and administrating adenosine. Adenosine is highly effective in PSVT control (especially PSVTs with fast rates) [Ballo *et al.* 2004], converting 60% of PSVTs to normal sinus rhythm within 1 min after a bolus injection of 6 mg and 92% after a bolus injection of 12 mg. Adenosine has rare side effects which usually resolve in less than 60 s [Blomstrom-Lundqvist *et al.* 2003]. Adenosine has been used safely in PSVT control in prehospital settings too [Gausche *et al.* 1994; McCabe *et al.* 1992]. Most adenosine-controlled PSVTs are feasibly maintained in sinus rhythm in acute care settings but there are still some cases of early recurrence. Different studies have been conducted to find better therapeutic modalities with a lower recurrence rate but studies on oral agents are rare.

Our study showed that oral verapamil can decrease the early recurrence of PSVT (after its successful control with intravenous adenosine) effectively while showing no significant adverse reactions. This can be due to enhanced negative chronotropic effects on the AV node resulting from interrupted AV nodal reentry pathways (adenosine effect) and reduced sinus node rate and AV nodal conduction (verapamil effect) [DiMarco, 2000; McAllister *et al.* 1983; Burkart, 1992; McTavish, 1989].

This negative chronotropic effect of calcium channel blockers (including verapamil) is

Table 1. Baseline data of patients in adenosine-only and adenosine/verapamil groups.

Variable	All patients (*n* = 92)	Adenosine only (*n* = 46)	Adenosine/ verapamil (*n* = 46)	*p* value
Age, mean (±SD), years	53.47 (±13.99)	50.22 (±14.56)	56.72 (±12.74)	0.14*
Sex, *n* (%)				0.83$
Male	53(57.6)	26 (56.5)	27 (58.6)	
Female	39 (42.3)	20 (43.7)	19 (41.3)	
Heart rate, beat per min	162.7 (±11.0)	162.9 (±9.8)	162.9 (±10.7)	0.85*
Systolic blood pressure, mean (±SD), mmHg	113.7 (±13.9)	114.4 (±12.44)	112.6 (±15.3)	0.76*
Diastolic blood pressure, mean (±SD), mmHg	80.4 (± 9.9)	82.2 (± 10.4)	78.5 (±9.2)	0.33*
Respiratory rate, mean (±SD), respiration per min	13.6 (±1.4)	13.6 (±1.6)	13.6 (±1.3)	0.14*
Arterial O_2 saturation, mean (±SD), %	97.5(±0.6)	97.5 (±0.6)	97.3 (±0.7)	0.41*
Comorbid condition, *n* (%)				0.26$
Diabetes mellitus	26 (28.2)	14 (30.4)	12 (26.0)	
Hypertension	34 (36.9)	18 (19.5)	16 (34.7)	
Ischemic heart disease	41(44.5)	20 (43.4)	21 (45.6)	
Obstructive lung disease	30 (32.6)	12 (26.0)	18 (39.1)	

*Student's t test.
$$\chi^2$ test.

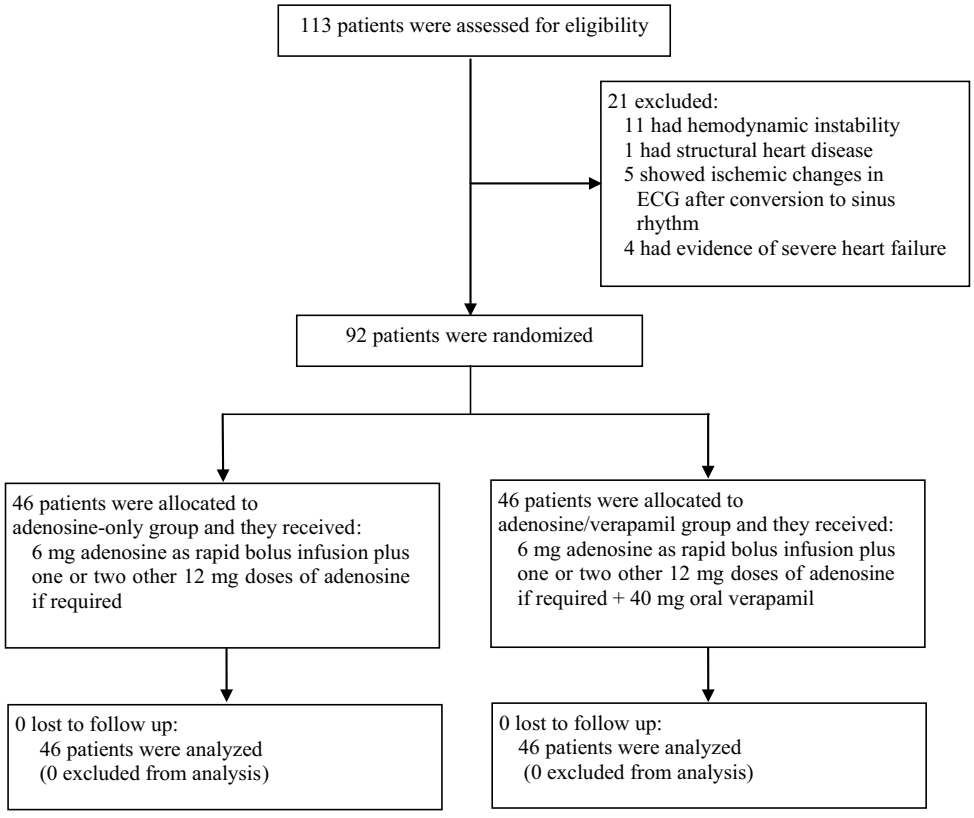

Figure 1. CONSORT diagram showing patient flow in study.
ECG, electrocardiogram.

relatively well known and most studies have shown that intravenous verapamil has similar efficacy to adenosine in PSVT control [Mangrum and DiMarco, 2002; DiMarco, 2000]. There are also other studies evaluating the role of the negative chronotropic effect of calcium channel blockers in PSVT control by focusing on their self-administration during well tolerated PSVT attacks. For example, a study on self-administration of a single dose of diltiazem/propranolol at the time of arrhythmia onset showed that this oral antiarrhythmic regimen can control infrequent, long-lasting and well tolerated PSVTs effectively, safely leading to decreased emergency room admissions [Alboni *et al.* 2001].

In another study by Yeh and colleagues a single oral dose of 120 mg diltiazem plus 160 mg propranolol terminated the electrically induced PSVT in 14 (93%) of 15 cases within 3 h of drug administration. In addition, 50 of 51 PSVT episodes occurring during 5 ± 1 months of follow up were converted within 3 h (conversion time 21 ± 16 min) after a single diltiazem plus propranolol oral dose with no major drug-related adverse effects [Yeh *et al.* 1985]. There are similar studies with other antiarrhythmic drugs like flecainide [Musto *et al.* 1992]. Some other studies have used calcium channel blockers to control the ventricular rate in patients with chronic atrial flutter or atrial fibrillation (in conjunction with digoxin) and in prophylaxis of repetitive paroxysmal supraventricular tachycardia [Mangrum and DiMarco, 2002].

Contrary to our study, Hamer and colleagues showed in their study of 10 patients with PSVT that oral verapamil could terminate the PSVT in one patient after 40 min and in two other patients after 90 min. They also did nuclear studies to evaluate oral verapamil absorption during PSVT and showed that gastric emptying time was increased during PSVT and serum verapamil level was lower in patients with PSVT than in patients with sinus rhythm [Hamer *et al.* 1987].

Limitations

The most important limitation in our study is that we did not used placebo. Other placebo-controlled studies may be more beneficial in identifying the role of oral verapamil in PSVT early recurrence control in the emergency department. Another limitation may be that we have only studied verapamil but not other calcium channel blockers like diltiazem. Our follow-up period is limited to 6 after administration and more prolonged follow ups may be considered in other studies. We have used the oral form of verapamil but the crushed sublingual form may be used too. According to some studies different factors like age, baseline heart rate and systolic blood pressure, known heart disease and rhythms encountered after adenosine administration can influence the recurrence of PSVT after its control with intravenous adenosine [Chun *et al.* 2002; Morrison *et al.* 2001; Luber *et al.* 2001] but we did not evaluate the role of these factors in our study.

Although our results showed that recurrence rates in the first 30 min after treatment were not statistically significant different in the two treatment groups ($p = 0.07$), this difference may be clinically important and shows a trend in the adenosine-only group to be better controlled. Oral verapamil reaches its peak plasma level 1–2 h after administration [John *et al.* 1992], thus the insignificance in PSVT control during the first 30 min could be due to the negligible blood level of verapamil, but we have no explanation for the better control of arrhythmia in the adenosine-only group. This could be an accidental finding and other more controlled studies are needed to clarify the true difference.

Conclusion

Adding oral verapamil to intravenous adenosine is an effective and safe approach to decreasing the early recurrence rate of PSVTs controlled with adenosine in the acute cardiac care setting. This therapeutic modality could help acute care physicians be more confident about maintaining the achieved sinus rhythm in successfully converted PSVTs.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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