

Clinical paper

Slow infusion of calcium channel blockers compared with intravenous adenosine in the emergency treatment of supraventricular tachycardia[☆]

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ABSTRACT

Introduction: The emergency treatment of supraventricular tachycardia (SVT) has, over the last two decades, changed from verapamil to adenosine primarily owing to documented hypotensive episodes occurring with rapid bolus infusions of the calcium channel blocker. Slow infusions of calcium channel blockers have not previously demonstrated hypotension to any significant degree. The aim of this study was to compare the efficacy and safety of bolus intravenous adenosine and slow infusion of the calcium channel blockers verapamil and diltiazem in the emergency treatment of spontaneous SVT.

Methods: A prospective randomized controlled trial with one group receiving bolus intravenous adenosine 6 mg followed, if conversion was not achieved, by adenosine 12 mg; and the other group receiving a slow infusion of either verapamil at a rate of 1 mg per minute up to a maximum dose of 20 mg, or diltiazem at a rate of 2.5 mg per minute up to a maximum dose of 50 mg. These infusions would be stopped at time of conversion of the SVT or when the whole dose was administered. Heart rate and blood pressure was continuously monitored during drug infusion and for up to 2 h post-conversion.

Results: A total of 206 patients with spontaneous SVT were analysed. Of these, 102 were administered calcium channel blockers (verapamil = 48, diltiazem = 54) and 104 were given adenosine. The conversion rates for the calcium channel blockers (98%) were statistically higher than the adenosine group (86.5%), $p = 0.002$, RR 1.13, 95% CI 1.04–1.23. The initial mean change in blood pressure post-conversion in the calcium channel blocker group was $-13.0/-8.1$ mmHg (verapamil) and $-7.0/-9.4$ mmHg (diltiazem) and $2.6/-1.7$ mmHg for adenosine. Only one patient in the calcium channel group (0.98%) (95% CI 0.025–5.3) developed hypotension, and none in the adenosine group.

Conclusion: Slow infusion of calcium channel blockers is an alternative to adenosine in the emergency treatment of stable patients with SVT. Calcium channel blockers are safe and affordable for healthcare systems where the availability of adenosine is limited.

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1. Introduction

Paroxysmal supraventricular tachycardia (SVT) is a common cardiac emergency presenting to the Emergency Department (ED). Since the 1970s intravenous verapamil has been the drug of choice^{1,2} for the treatment of SVT. The 1986 American Heart Association guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care recommended that verapamil be given as a 2.5–5 mg intravenous bolus over 2 min and 5–10 mg over 2 min to be given after 15–30 min of the first dose if the SVT persisted³ or recurred and if blood pressure remains acceptable. For the 1992 Ameri-

can Heart Association Guidelines, adenosine was recommended as the initial drug of choice for haemodynamically stable paroxysmal SVT. The sequence of agents recommended was adenosine twice (6 mg followed by 12 mg). If the blood pressure had not dropped and the SVT persisted up to two doses of verapamil (2.5–5 mg) intravenous over 2 min followed by 5–10 mg over 2 min could be given. When treating the elderly or when blood pressures were within the lower range of normal, smaller doses (2–4 mg) of verapamil over a longer period (3–4 min) were recommended for the first dose.⁴ The main reason given for adenosine as the first choice drug was that adenosine does not cause hypotension to the same degree as verapamil because adenosine has a very short half-life (<10 s).

A previous randomized controlled trial (161 patients) by our group compared intravenous verapamil and intravenous diltiazem⁵ given as slow infusions (verapamil at a rate of 1 mg per minute and

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diltiazem at a rate of 2.5 mg per minute). This showed a conversion rate of more than 97% with only one patient (1%) developing hypotension. This finding suggests that the haemodynamic instability previously attributed to verapamil may be related to the speed of verapamil administration.

There are few studies directly comparing the effectiveness of adenosine and calcium channel blockers. Most of these studies recruited subjects with laboratory-induced SVT.^{6–8} In addition, they used a rapid bolus of intravenous calcium channel blocker given over 15 s (except for the study by Hood and Smith).⁷ These studies generally conclude that adenosine and verapamil are both highly effective in the termination of SVT.

There has been no previous large prospective, randomized controlled trial comparing the usefulness of intravenous adenosine vs. slow-infusion calcium channel blockers in a clinical patient-care environment. The aim of this study was to compare the efficacy and safety of bolus intravenous adenosine with the slow infusion of verapamil or diltiazem, in the termination of spontaneous SVT in the ED.

2. Methods

This was a prospective, randomized, controlled clinical trial in patients presenting with SVT to an ED. The study was approved by the hospital Ethics Committee.

2.1. Patients

Patients of at least 10 years of age, who presented to the ED of the Singapore General Hospital with a regular narrow complex tachycardia and an electrocardiographic (ECG) diagnosis of SVT, not converted by vagal manoeuvres (Valsalva manoeuvre or carotid sinus massage or both) and who were in SVT at when seen by a doctor were included in the study.

The exclusion criteria were:

- Patients with signs of impaired cerebral perfusion (e.g. altered mental state) or acute pulmonary edema.
- Patients with a subsequent diagnosis of arrhythmias other than SVT (i.e. sinus tachycardia, atrial flutter, atrial fibrillation or idiopathic ventricular tachycardia) were excluded from the analysis if they were initially enrolled.
- Pregnancy by history (urine pregnancy testing was not used to actively exclude the condition in any of the female patients entered into the study).

2.2. Protocol

Once consent was obtained, patients were randomly assigned into two treatment arms:

- The calcium channel blocker group: patients randomized to receiving diltiazem as the first choice were administered diltiazem at a concentration of 0.625 mg/ml by slow intravenous infusion at a rate of 4 ml per minute (equivalent to 2.5 mg per minute) up to a maximum dose of 50 mg. Those randomized to receiving verapamil as the first choice were administered verapamil at a concentration of 0.25 mg/ml by slow intravenous infusion at a rate of 4 ml per minute (equivalent to 1 mg per minute) up to a maximum dose of 20 mg. Both infusions were given using a Terumo infusion pump. During intravenous infusion, the patient's vital signs (heart rate, systolic and diastolic blood pressures) were monitored using a Propaq[®] vital sign monitor at 2-min intervals up to the completion of infusion or conversion from SVT, whichever was the earlier. At the time of

conversion to sinus rhythm, the infusion was stopped and the amount of drug infused recorded.

- The adenosine group were administered adenosine as a rapid bolus within a 2 s time frame through an 18G intravenous cannula placed in the antecubital fossa, followed by a 10 ml saline push and elevation of that upper limb. Initially a 6 mg bolus was administered, and if there was no conversion of the SVT within 2 min of the administration, a further 12 mg bolus was administered.

If the SVT was not converted by the end of the verapamil or diltiazem infusion, the patients in these groups were then given intravenous adenosine as described above. For patients randomized to receive adenosine initially, and remaining in SVT after the first two boluses, they were again randomized to receive either verapamil or diltiazem slow infusion as described above.

There were four treatment arms as follows:

1. Verapamil infusion → adenosine
2. Diltiazem infusion → adenosine
3. Adenosine → verapamil infusion
4. Adenosine → diltiazem infusion

Patients were randomized using sealed envelopes. Each of these four choices were written on a card and placed in a sealed envelope. The nurse in charge of patients would perform the randomization by drawing the serialized sealed envelope to decide the order of treatment.

If the tachycardia was not converted at the end of the study protocol, patients were managed with synchronized electrical cardioversion if the patient was haemodynamically unstable, or further pharmacotherapy if the patient was haemodynamically stable. This was at the discretion of the treating physician.

Following successful conversion, patients were closely monitored for the next 30 min with measurement of vital signs at 1 min (immediate post-conversion), 5, 10, 15 and 30 min post-conversion, following which, if they remained stable, they were monitored for 2 h in the Department's Emergency Observation Ward with telemetry. If there were no recurrences during the period of observation, they were discharged with an appointment to attend the Cardiology Department's Arrhythmia Clinic within a week. Patients with recurrence of SVT during the 2-h observation period were managed at the discretion of the treating physician.

Follow-up records of the Department of Cardiology were reviewed for a period of up to 1 year.

2.3. Statistical analysis

The association between the success rate of conversion with slow verapamil or diltiazem infusion and adenosine bolus was assessed using chi-square or Fischer's exact test. Normality assumptions of the quantitative variables (age, blood pressure and heart rate) was checked using the Kolmogorov Smirnov 1 sample test. Differences within treatment groups were assessed using paired *t*-tests if normality assumptions were satisfied; otherwise the Wilcoxon Signed Rank test was applied. Differences between treatment groups were determined using ANOVA or Kruskal–Wallis tests with bonferroni adjustments applied. Statistical significance was set at $p < 0.05$.

2.4. Sample size calculation

Our local studies on conversion of spontaneous SVT showed that:

Table 1
Pre-treatment patient characteristics.

	Calcium channel blockers group			Adenosine group (n = 104)	Remarks
	Verapamil (n = 48)	Diltiazem (n = 54)	Total (n = 102)		
Mean systolic BP ± S.D. (mmHg)	117.7 ± 26.1	117.1 ± 28.2	117.4 ± 27.1	114.8 ± 27.9	p = 1.0
Mean diastolic BP ± S.D. (mmHg)	75.0 ± 14.9	78.1 ± 18.7	76.7 ± 17.0	78.7 ± 20.9	p = 1.0
Initial heart rate (beats per minute) ± S.D.	172.9 ± 30.2	176.8 ± 24.1	174.6 ± 27.1	172.5 ± 33.2	p = 0.650
Duration of SVT (h) ± S.D.	7.13 ± 5.26	2.93 ± 1.97	5.10 ± 4.51	4.37 ± 7.14	p = 0.095
Males (%)	40	40	40	42	p = 0.880
Mean age (years) ± S.D.	47.7 ± 19.	48.9 ± 18.3	48.3 ± 18.6	50.6 ± 17.0	p = 0.614

Success rate of adenosine is 83% (20/24)⁹ and
Success rate of calcium channel blocker is 97% (157/161)⁵

However, about 15% of “narrow regular complex” tachycardia, we enrolled were found to have subsequent diagnoses of arrhythmia other than SVT (i.e. tachycardia, atrial flutter, atrial fibrillation or idiopathic ventricular tachycardia). Hence we planned to enroll 115 patients on each arm (calcium channel blockers vs. adenosine).

3. Results

From 1st January 1997 to 31st March 1999, over a 27-month period, a total of 236 patients with regular narrow complex tachycardia not converted by vagal maneuvers were treated by, the Singapore General Hospital ED. Of these, none were pregnant by clinical history, and 3 had signs of impaired cerebral perfusion or heart failure. All three had concomitant medical problems and all were converted with 6 mg IV bolus of adenosine. The remaining 233 patients were enrolled into the trial.

Twenty-seven patients were excluded from analysis as they were found not to have SVT after enrollment. 20 had atrial fibrillation and 7 had sinus tachycardia. The number of eligible patients for statistical analysis was 206. Of these 102 were in the calcium channel blocker group and 104 in the adenosine group.

The pre-treatment characteristics of these patients are given in Table 1. There were no significant differences between the groups.

Fig. 1 shows the conversions for the different treatment arms used in the trial. 47 of the 48 (97.9%) who received verapamil infusion were converted with a mean dose of 6.5 mg (S.D.: 4.5 mg). One patient, a 57-year old previously healthy man, presented with a 1-week history of palpitations and a pre-treatment blood pressure of 122/81 mmHg developed hypotension (74/61 mmHg) after 7.5 mg of verapamil infusion. His SVT was terminated by synchronized cardioversion, following which his blood pressure improved to 103/69 mmHg. Fifty-two out of 53 patients (98.1%) who received diltiazem infusion were converted with a mean dose of 16.9 mg (S.D.: 13.7). The one patient who was not converted with the diltiazem infusion, was successfully converted with a 6 mg bolus of adenosine.

Of the 104 patients treated with adenosine, 69 (66.3%) were terminated with a 6 mg bolus dose and a further 21 (20.2%) converted after an additional 12 mg dose of adenosine. The total conversion rate with adenosine was 86.5%.

Of the 14 patients not converted by 6 and 12 mg of adenosine, 9 were successfully converted with verapamil infusion and 5 with diltiazem infusion. One of these patients with a pre-treatment blood pressure of 85/46 mmHg and treated with adenosine followed by verapamil developed a further drop in blood pressure (BP 78/44 mmHg) after infusion of 13 mg of the drug and successful

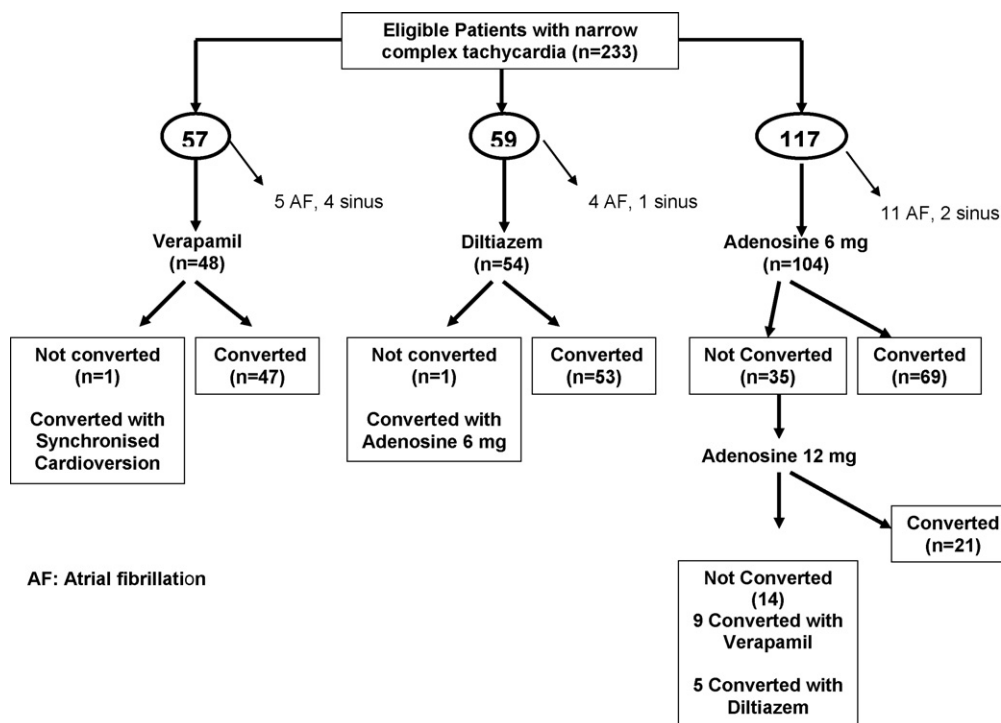


Fig. 1. Results of treatment of SVT patients.

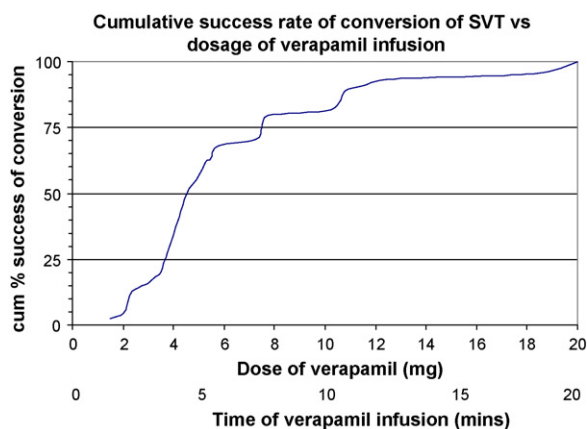


Fig. 2. Cumulative success rate of conversion of SVT vs. dosage of verapamil infusion.

conversion to sinus rhythm. The blood pressure gradually recovered to 104/51 mmHg within 1 h. Two-dimensional echocardiography 2 days later demonstrated a dilated cardiomyopathy with an ejection fraction of 14%.

The success rate of calcium channel blocker infusion (98%) was statistically greater than for adenosine (86.5%), p -value = 0.002 and RR 1.13 (95% CI 1.04–1.23). For every 9 (number to treat) patients treated with calcium channel blocker infusion, there was one additional conversion compared with adenosine (95% CI 8–10). The number needed to harm (hypotension) for calcium channel blocker infusion was 53 (95% CI 15–91).

None of the patients in the verapamil group had recurrences during the 2-h observation period. One patient from the diltiazem group and two from the adenosine group had recurrences during the 2-h observation period. The patient from the diltiazem group was converted with 150 mg intravenous amiodarone. One of the patients in the adenosine group was converted by 10.5 mg of verapamil infusion and the other recurrent SVT terminated spontaneously without any treatment.

The dose–response curves for verapamil and diltiazem for successful termination of SVT are shown in Figs. 2 and 3, respectively. The success rate of conversion of SVT increases with dosage of calcium channel blockers. The doses required to convert 25, 50 and 75% of SVTs were 15 ml (3.81 mg), 20 ml (5.00 mg) and 31 ml (7.69 mg)

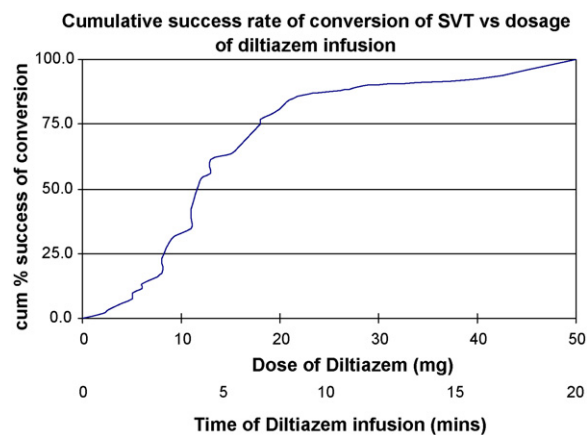


Fig. 3. Cumulative success rate of conversion of SVT vs. dosage of diltiazem infusion.

respectively for the verapamil infusion and 15 ml (9.38 mg), 20 ml (12.50 mg) and 29 ml (18.13 mg) for the diltiazem infusion.

For the group randomized to receive verapamil infusion, 80% required less than 10 mg of verapamil infusion for conversion. For the group randomized to receive diltiazem infusion, 88% required less than 25 mg of diltiazem for conversion.

The post-treatment vital signs are shown in Table 2. In the verapamil and diltiazem groups there were significant decreases in mean systolic blood pressure (13.0 mmHg in the verapamil group and 7.0 mmHg in the diltiazem group, p = 0.003 and 0.033, respectively) and mean diastolic blood pressure (8.1 mmHg in the verapamil group and 9.4 in the diltiazem group, p = 0.001 and p < 0.001, respectively). In the adenosine group there was no significant change in mean systolic blood pressures (+2.6 mmHg, p = 0.295) or mean diastolic pressure (of –1.7 mmHg, p = 0.447) in the immediate post-conversion phase.

The blood pressure changes in each of the groups were transient as the blood pressure gradually reverted to pre-treatment systolic blood pressures over the next 30 min (Table 3) in all groups. The diastolic pressures continued to remain below pre-treatment levels in all groups with patients remaining asymptomatic.

Eight patients had a medical history of bronchial asthma on active follow-up. Four patients (two on treatment with theophylline) in the adenosine group and another four patients (two on

Table 2
Immediate post-treatment vital signs.

	Calcium channel blockers group		Adenosine group	Remarks
	Verapamil	Diltiazem		
Number of patients	48	54	104	
Numbers converted with initial treatment	47 (98.0%)	53 (98.1%)	90 (86.5%)	p = 0.002 (Fisher's exact test). Both verapamil and diltiazem more likely to convert (RR = 1.13, 95% CI 1.04–1.23) compared to adenosine
Systolic BP (mmHg) (mean \pm S.D.)	104.6 \pm 17.0	109.4 \pm 18.7	117.9 \pm 24.4	p < 0.001 (Anova) Post hoc analysis Verapamil vs. diltiazem: p = 0.789 Verapamil vs. adenosine: p = 0.002 Adenosine vs. diltiazem: p = 0.064
Diastolic BP (mmHg) (mean \pm S.D.)	66.8 \pm 13.6	68.4 \pm 11.0	77.0 \pm 18.6	p < 0.001 (Anova) Post hoc analysis Verapamil vs. diltiazem: p = 1.0 Verapamil vs. adenosine: p < 0.001 Adenosine vs. diltiazem: p = 0.005
Heart rate (mean \pm S.D.)	91.9 \pm 11.3	90.2 \pm 17.2	99.4 \pm 18.5	p = 0.008 (Anova) Post hoc analysis Verapamil vs. diltiazem: p = 1.0 Verapamil vs. adenosine: p = 0.045 Adenosine vs. Diltiazem: p = 0.005

Table 3

Mean blood pressure changes during initial 30 min monitoring after conversion.

	Calcium channel blockers group		Adenosine group	Remarks
	Verapamil	Diltiazem		
Mean blood pressure pre-conversion (mmHg)	117.7/75.0	117.1/78.1	114.8/78.8	$p = 1.0/p = 1.0$
Mean blood pressure at conversion (mmHg)	104.6/66.8	109.4/68.4	117.9/77.0	$p < 0.001/p < 0.001$
Blood pressure 5 min after conversion (mmHg)	104.3/66.6	112.4/69.4	117.6/76.9	$p = 0.002/p < 0.001$
Blood pressure 10 min after conversion (mmHg)	107.1/66.7	112.9/70.5	115.35/75.1	$p = 0.068/p = 0.002$
Blood pressure 15 min after conversion (mmHg)	103.0/63.9	111.6/70.5	113.6/74.1	$p = 0.021/p = 0.002$
Blood pressure 30 min after conversion (mmHg)	104.2/65.3	114.4/70.8	112.2/71.2	$p = 0.033/p = 0.055$

treatment with theophylline) in the calcium channel blocker group. None of these patients had problems with conversion with the first drug used, though the two patients given adenosine both required 6 followed by 12 mg of the drug for conversion. None of these patients developed an acute asthma attack during the treatment of the SVT.

The cost calculations for the drugs used in this study are shown in Table 4. These calculations were confined to the phase of conversion of the SVT to sinus rhythm. This assumes that all other costs are the same. These figures show that the average cost of converting a patient from SVT to sinus rhythm with adenosine was more than double the cost with verapamil, with the cost of diltiazem midway between the two.

4. Discussion

Verapamil, diltiazem and adenosine compounds exert their maximum effect on the AV node by lengthening intranodal conduction time significantly.^{10,11} The effect of calcium channel blockers on paroxysmal SVT has been best studied with verapamil. Early studies suggest that adequate dosage of verapamil resulting in an initial plasma concentration exceeding 72 ng/ml is needed to effect conversion.¹² These concentrations were then achieved by giving bolus doses of verapamil at 0.075–0.15 mg/kg body weight.

Subsequently studies conducted with verapamil, either in the clinical or laboratory environment have tended to administer verapamil at doses of 5–10 mg (0.075–0.15 mg/kg body weight for a 70 kg patient) over 15–30 s and if no response was observed to repeat a further dose within 5–10 min.²

In 1971, it was demonstrated that intravenous diltiazem can also terminate narrow complex paroxysmal SVT.¹³ Two major studies^{14,15} using bolus doses of 150 µg/kg given intravenously over 2 min demonstrated the effectiveness and safety of diltiazem in the emergency management of paroxysmal SVT.

There have been several trials of bolus intravenous adenosine with bolus doses of intravenous verapamil either in the electrophysiology laboratory, in the clinical ED environment or in the pre-hospital arena.^{6,8,16–18} Most of these have affirmed the equivalent

efficacy of verapamil and adenosine in the initial conversion of SVT. Adenosine is frequently accompanied by transient side effects (facial flushing, chest discomfort, breathlessness in up to 75% of subjects), and a recurrence rate for SVT varying from 9 to 57%.^{7,9,18,19} The high recurrence rate may decrease the absolute conversion of SVT. The recurrence rate of our study was only 2.2% (2/90). Verapamil, can cause hypotension, when given in rapid bolus doses.^{1,7,18} A small study of 25 patients by Hood and Smith comparing bolus intravenous adenosine and verapamil at a rate of 1 mg/min up to a maximum of 15 mg demonstrated equivalent efficacy of both agents with a conversion rate of 100% for adenosine, and 73% for verapamil ($p = \text{NS}$).⁷ Hypotension was documented in one patient given verapamil (9.1%). The transient side effects with adenosine were common (76%).

Our study comparing slow infusions of two calcium channel blockers with adenosine shows that the routine use of a calcium channel blocker (either verapamil or diltiazem) in the emergency management of supraventricular tachycardia can still be justified. The caveat, though, is that the calcium blocker should be administered as a slow infusion (1 mg per minute for verapamil up to a maximum of 20 mg, or 2.5 mg per minute for diltiazem up to a maximum of 50 mg) with close blood pressure monitoring until conversion to sinus rhythm is achieved or the drug infusion is completed.

The fall in blood pressure produced by calcium channel blocker infusion is transient in most cases. This study has shown that slow infusion of calcium channel blockers enables the minimum dosage of drug to be delivered, just sufficient to convert each individual episode of SVT. Treatment of SVT can therefore be individualized.⁵ Higher doses of verapamil or diltiazem can be safely administered by the slow-infusion mechanism without the undue fear of significant hypotension.²⁰ The occasional patient who has a significant drop in blood pressure, especially with symptoms, can be treated with a slow infusion of calcium chloride or calcium gluconate.²¹

Our two patients on theophylline required a 6 mg followed by 12 mg dose of adenosine. The numbers are too small to determine

Table 4

Cost of treatment.

	Calcium channel blockers group		Adenosine group	Remarks
	Verapamil	Diltiazem		
Number of patients	48	54	104	
Numbers converted with initial treatment (%)	47 (98.0%)	53 (98.1%)	90 (86.5%)	
Unit cost of drug	\$1.40 per 5 mg vial	\$15 per 50 mg vial	\$20 per 6 mg vial	
Number of vials needed (mean and range)	4	1	1 for 66% and 3 for 34%	
Cost of meds per patient (mean and range)	\$5.60	\$15.00	\$20 × 0.66 + \$60 × 0.34 = \$33.60	
Cost of accessories (needles and pumps)	\$4.00	\$4.00	\$1.00	
Time taken for conversion	6.5 min	6.76 min	1.48 min	
Cost of staff time to conversion	\$6.50	\$6.76	\$1.48	Calculated at \$1.00 per min
Cost before crossover	\$16.10	\$25.76	\$36.08	
Cost of crossover	Sync DC shock = \$12.50 × 1/48 = \$0.26	\$20 × 1/54 = \$0.37	9/104 × \$16.10 + 5/104 × \$25.76 = \$2.63	
Total cost for conversion	\$16.36	\$26.13	\$38.71	

Note: 1. All cost calculations are in Singapore dollars (SIN \$1.65 = US \$1.00). 2. "Conversion" refers to conversion of SVT to sinus rhythm.

whether this was due to theophylline blocking the action of adenosine.

There are many areas in the world where intravenous calcium channel blockers, especially verapamil, are still being used as first line treatment of spontaneous stable SVTs as intravenous adenosine is not available. In these circumstances, we recommend the calcium channel blockers be administered as a slow infusion or slow bolus—at a rate of 1 mg per minute for verapamil.

For institutions where infusions of calcium channel blockers and bolus intravenous adenosine are both available for the treatment of stable SVT, the patient should be fully informed of the pros and cons of both options, i.e., high incidence of minor but unpleasant side effects in patients treated with adenosine and the small potential of hypotension after calcium channel blocker infusion.²²

5. Conclusion

Calcium channel blockers administered as a slow infusion offer an alternative to adenosine in the emergency treatment of stable SVT patients. In our study slow calcium channel blocker infusions were more effective than bolus IV adenosine 6 mg followed by 12 mg in converting stable spontaneous SVT. Calcium channel blockers are safe and affordable for healthcare systems where the availability of adenosine is limited.

Conflict of interest statement

We hereby declare that there is no conflict of interest in conducting this randomized clinical trial.

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