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Original Research

A Non–Blinded, Randomized Controlled Trial Of The AHA Versus The Simplified Method Of Administration Of Adenosine In The Treatment Of Adult Patients With Stable Re-Entry Supra-Ventricular Tachycardia, Tshwane, South-Africa

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Abstract

Introduction: Adenosine is recommended for the treatment of supraventricular tachycardia (SVT). Administration is via a stopcock where adenosine and a flush are given, often resulting in mishaps. The aim of this study was to compare a simplified method of administration (SIM) to the American Heart Association (AHA) method.

Methods: A randomized controlled trial (RCT) was conducted in Tshwane from 2015 to 2020. A 2:1 randomization procedure of the SIM vs. AHA method was followed. Thirty-three patients were randomized, eight to the AHA and 25 to the SIM group.

Results:

Success rate for the AHA group was 71% (95% CI 0.38-1.05) and 74% for the SIM group (95% CI 0.56-0.92) Chi square p=0.897. Failure rate of the AHA group was 29% and 26% for the SIM group. Chi square p=0.897.

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We tested non-inferiority with a lower limit delta of 10%. The 90% two-sided CI, i.e. 95% one sided of SIM – AHA: (90% CI -0.294- 0.344) had a lower limit of less than -0.10. SIM could therefore not be shown as non-inferior to the AHA.

Conclusion: Although conversion rates in the two groups was similar, the SIM method could not be shown as non-inferior to the AHA method due to the sample size. Ease of administration without an additional assistant or stopcock favour the SIM method.

Key words: Adenosine, Supraventricular tachycardia, administration method, cardioversion, vagal maneuvers, saline flush

Introduction

Re-entry SVT due to nodal and extra-nodal re-entry mechanisms is an arrhythmia that emergency physicians are expected to treat independently. The incidence is around 35 per 100 000 per year, with a prevalence of 2.25 cases per 1000 in the general population of the United States of America.[1] Intravenous adenosine is recommended for the treatment of hemodynamically stable, regular, narrow complex SVT by the American Heart Association (AHA) when the SVT does not respond to vagal manoeuvres. The initial recommended dose for adult patients is 6 mg over 1-3 seconds through a large vein, followed by a 20 ml normal saline (NS) flush. Thereafter, if there is failure of conversion, a subsequent dose is increased to 12 mg also followed by a 20 ml saline flush[2]. An additional adenosine dose with a third dose of 12 mg is recommended in the AHA journal by Page RL et al.[3] Our study like the McDowell study[4] used the three dose method and not the two dose from the ACLS[2] manual. It has also been shown to be safe in unstable patients with re-entry SVT, where instability was defined as patients with a blood pressure of less than 90 mm Hg, pulmonary oedema, chest pain or an altered mental status. Even in these patients, one dose is recommended while preparations are made for cardioversion. The AHA technique requires the intravenous (IV) line to be connected to a three-way stopcock and training and co-ordination to be successful. Problems arise when the NS flush inadvertently enters the adenosine syringe upon injection leading to disconnection of the syringes and intravenous fluids spraying outside the line. Such is the complexity of the procedure that the Advanced Cardiac Life Support Instructors in South-Africa often recommend that a second person should assist to stabilize the syringe connections during injection.[5] Moreover, three way stopcocks are a resource that are not always available in settings in which adenosine may be administered such as in EMS services and small, poorly resourced emergency centres (ECs). It may even run out of stock in some of the better resourced ECs. In this regard, South-Africa and other Southern-African countries which are considered low to middle income countries where additional resources are frequently a practical issue for clinicians working on the EC floor.

The aim of this study was to compare the failure and success rates of conversion of a re-entry SVT to NSR[3] of the simplified single syringe technique with diluted adenosine (SIM) to the AHA method. A number of studies have shown that Adenosine is stable inside saline, Ringer's lactate and dextrose.[6,7] The rationale for using a non-inferiority methodology was that although the AHA two syringe method has been proven to be effective for termination of re-entry SVTs, it's a bit ungainly and requires training and co-ordination. If the SIM method could be shown to be non-inferior, it would offer simplicity of administration without the need for extra devices such as a three way stop cock and/ or an assistant during administration.

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Methods

This study is a non-inferiority parallel group RCT. The trial was started in 2015 after approval was obtained from the Research Ethics Committee, Faculty of Health Sciences, University of Pretoria which complies with the principles of Helsinki. The trial was temporarily stopped after a year to make amendments to the protocol for which ethical approval was obtained. These amendments included capturing more baseline characteristics of the participants, and appointing a senior Emergency Medicine (EM) specialist to review the ECG and confirm that it was in fact a re-entry SVT prior to randomization and administration of adenosine. This protocol adjustment was considered an additional safety step based on the first few cases in which some of the enrolling clinicians felt uncertain about the accuracy of their diagnosis of re-entry SVT.

Patients were recruited from two tertiary academic hospitals located in Tshwane for the study. Patients presenting to the ECs as well as those admitted to the cardiology/internal medicine units were approached for inclusion to the study.

Eligible participants were between the ages of 18 and 85 and had to have two failed vagal manoeuvre attempts to convert their re-entry SVTs back to NSR. Their ECGs had to be validated as a re-entry SVTs by an Emergency Medicine specialist.

Participants were excluded if they were too unstable to give informed consent, had a known allergy to adenosine, recently ingested dipyridamole, carbamazepine, theophylline or caffeine in the preceding two hours. Patients suffering from an acute asthma attacks or who had a heart transplant were excluded from the study.

Both methods used adenosine as recommended by the AHA for the dose, route, indications and contra-indication for treating re-entry SVT. The recommended doses of 6 mg, followed by 12 mg repeated once if termination of re-entry SVT was unsuccessful after 2 minutes was used. Both methods used the intravenous route via a large bore cannula. Both methods were given as rapid pushes over 1 to 3 seconds.

The AHA method involved drawing up adenosine dose (6 or 12mg) with a flush of 20ml NS in 2 separate syringes. Both syringes were attached to the IV injection port closest to the patient and the IV tubing was clamped above the injection port. The IV adenosine was pushed as quickly as possible over 1-3 seconds. While maintaining pressure on the emptied adenosine plunger, the NS flush was pushed as rapidly as possible, immediately after the adenosine. This was followed by unclamping of the IV tubing.

The SIM method was also very similar to the AHA except for the drawing up adenosine (6 or 12 mg) in a 20 ml syringe and then adding normal saline to fill the syringe to 20 ml. The mixture was attached to the IV injection port closest to the patient and the IV tubing above the injection port was clamped. The mixture was given as a single rapid push over 1- 3 seconds. This method was performed without a three-way stopcock.

The objectives of the study were to establish the failure and success rate of the SIM method vs the AHA method to terminate a re-entry SVT. The H0 (Null Hypothesis) being that a SIM method of IV adenosine administration is inferior to the standard AHA method of IV adenosine administration. H1 (Research Hypothesis) is that a simplified method of IV adenosine administration is not inferior to the standard AHA method of IV adenosine administration.

The primary outcome of this trial was defined as successful conversion of the re-entry SVT to NSR, which must be sustained for at least 10 minutes.[3] Secondary outcomes were failed conversion

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defined as a persistent re-entry SVT, conversion to another arrhythmia, or a NSR that lasted less than 10 minutes. Outcomes were assessed by the treating physician who administered the adenosine doses and were documented in the data collection forms. All treating clinicians were trained on the trial protocol prior to commencement of the study.

A defibrillator was used to print a rhythm strip of standard lead II of the re-entry SVT seconds before the administration of adenosine and left to print at least 10 seconds post administration. A 12-lead ECG was done after the administration of Adenosine to compare with the ECG done prior the administration.

The following assumptions was made in calculating the sample size: a response rate of 90% efficacy for both methods, a noninferiority delta of -10% and a 95% one sided confidence interval. Chi square statistical anlysis was used to calculate the p-values for primary and secondary outcomes. The study was truncated after 5 years due to a very slow enrolment rate because of an initial overestimation of the frequency of stable SVTs. Only 33 (instead of 151 for a power of 80% and alpha set at 0.05) patients could be enrolled with 25 in the SIM and 8 in the AHA arms, which resulted in an estimated power test of 59.08%.

The main factor that affected recruitment rate was rarity of the condition with stable patients. As a result, the trial was stopped on the 16th of December 2020 in liason with the ethics committee and officially on the Protocol Registration and Results System ClinicalTrials.gov.

Eligible patients were randomly assigned in a 2:1 ratio to receive adenosine via the SIM method or to usual care as recommended by the AHA (see descriptions below) therefore for every 2 patients randomized to the SIM method of giving adenosine, 1 patient was randomized to the AHA method. The reason for this randomization was the anticipated low incidence of re-entry SVTs.

Randomisation was done using consecutively numbered opaque envelopes with instructions of either one of the two methods of adenosine administration. Envelopes were checked daily to confirm that they were not opened and that they were used in sequence. Each of the two institutions received a separate batch of numbered and sealed envelopes with instructions to which treatment arm the participants were allocated. The envelopes in each batch were manually scrambled and then numbered to create a random sequence. Each institution received a batch of 99 envelopes consisting of 66 SIM and 33 AHA.

The treating physician who identified a stable patient with re-entry SVT enrolled the participants. The EM specialist would confirm the rhythm; thereafter the treating physician could open the allocation envelope and assign participants to one of the two interventions.

The full trial protocol can be accessed on www.clinicaltrials.gov – registration number NCT04392362.

Results

Thirty-three patients were randomized to the trial of which 25 was randomized to the SIM method and 8 to the AHA method. Of the 25 patients randomized to the SIM method, 2 self-converted to NSR before Adenosine administration. Of the 8 patients randomised to the AHA method, 1 self-converted prior to Adenosine administration. Because the intervention being investigated could not be applied to these three patients, they were excluded from the trial, leaving 23 in the SIM group and 7 in the AHA group.

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This resulted in a 3:1 randomization rather than the planned 2:1 randomization. The skewed randomization is likely a random effect as a result of the fact that the trial was truncated due to low recruitment and would have balanced out if more patients were recruited.

The overall success rate for the AHA group was 71% (95% CI 0.38-1.05) and 74% for the SIM group (95% CI 0.56-0.92). The p-value calculated with Chi-square was p=0.897. The failure rate of the AHA group was 29% and 26% for the SIM group (p=0.897). We tested for non-inferiority with a lower limit delta margin of 10%. When using the 90% two-sided CI, i.e. 95% one sided of SIM – AHA: (90% CI -0.294- 0.344) had a lower limit of less than -0.10. The SIM could therefore not be shown to be non-inferior to the AHA and the null hypothesis could not be rejected.

The relative risk (RR) was calculated at 0,9130 with a 95% CI of 0,2347 to 3,5517. The RR for noninferiority should be no lower than 0,9 if the non-inferiority threshold is -10%. Although the overall RR > 0.9 the lower limit of the confidence interval of the RR was 0.2347, which crossed the margin of 10% and was lower than 0.9 and therefore non-inferiority could not be confirmed. There were no deaths reported from either of the groups related to the study interventions.

Discussion

Due to the small sample size of our study it was too underpowered to determine inferiority vs. noninferiority of the SIM method. This was the major limitation of our study. Hence the study can be viewed as a pilot study. Although we found a similar overall and first dose success rate between the SIM and AHA groups, this result should be interpreted with caution due to the already mentioned low sample size. A further limitation to our study is the skewed randomization of 3:1 as opposed to the planned 2:1 randomization. The fact that the control group had a lower number of patients may therefore have skewed the outcome in that group, as one or more positive or negative outcome(s) could have had a potentially significant statistical effect. A further limitation was that the site of the IV access was not documented as more proximal versus distal access, which may have been a confounding factor in conversion. No patients received adenosine through a central line.

Our study is comparable to those of Choi et al.[8] and McDowell et al.[4] McDowell et al.[4] used a single syringe (SS) method using 18ml NS to dilute adenosine and compared it to the two-syringe (TS) method. This was a prospective observational, non-randomized, non-inferiority study with a sample size of 53 patients. First-dose success to SR was higher in the SS group at 73.1% compared to 40.7% in the TS group (NI p=0.0176). They also reported a higher success rate in the SS group (100%) with repeated doses of adenosine compared to 70.4% in the TS group (NI p=0.0043). They did not randomize their patients.

Choi et al.[8] used a single syringe (SS) method using 15 ml NS to dilute adenosine and compared it to a two syringe (TS) technique. This study was a randomized, non-blinded study and had a sample size of 65 patients. There was no difference in successful termination of re-entry SVTs with 80 and 85.7% for the SS and TS method (p=0.39) respectively. They did not report first- dose success rates.

Our study is generalizable to patients seen in ECs or wards with re-entry SVT. It had a spectrum of co-morbidities often seen in patients with re-entry SVT. The REVERT[9] trial and Shaker et al.[10] had a similar spectrum of co-morbidities for the re-entry SVT patients they enrolled in their studies. The treatment method that was investigated is feasible and easy to implement as it is a simplification of the existing technique and requires no additional equipment. In fact, adjuncts such as 3-way stopcocks or an assistant are unnecessary with the SIM method.

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Several studies have shown that adenosine remains stable in NS.[6,7] This implies that adenosine would not undergo any chemical degradation when pre-mixed with a saline flush and supports the theoretical concept that adenosine can be pre-mixed with a carrier fluid or flush.

The concept has also gained ground on free open-access medical education platforms which has advocated for combining an adenosine dose and saline flush together. Hayes[11] already promoted this concept in 2012 and updated his recommendations in 2019. Scott Weingart promoted a similar concept in 2015 on his popular podcast-based website called EMCrit.[12]

Of note in our trial, is that success rates to NSR were only achieved with the first two doses of adenosine and none with a 3rd dose. This finding lends supports the 2015 ACLS manual[3] recommendation of only giving up to 2 doses of adenosine.

Due to truncation of the sample, randomisation was not completely successful. A randomization of 2:1 could have been achieved if a total of 99 envelopes were used. But only 33 were used.

This is the first study of its kind in Africa and although no patients were harmed in the trial, our study was underpowered to make inferences to the general population.

Conclusion:

Conversion of re-entry SVT to NSR in the SIM and AHA groups were similar, but this result should be interpreted with caution due to the low sample size. In our study, the SIM method could not be shown to be non-inferior to the AHA method due the small sample size. This study can therefore be viewed as a pilot study pending a larger trial or could form part of a meta-analysis of smaller trials. The SIM administration method of intravenous adenosine for the conversion of re-entry SVT to NSR is a more convenient method of drug administration. The authors therefore recommend the use of the SIM (single syringe) method but, to prove non-inferiority and/or superiority a larger RCT or metaanalysis is required.

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Tables and Figures

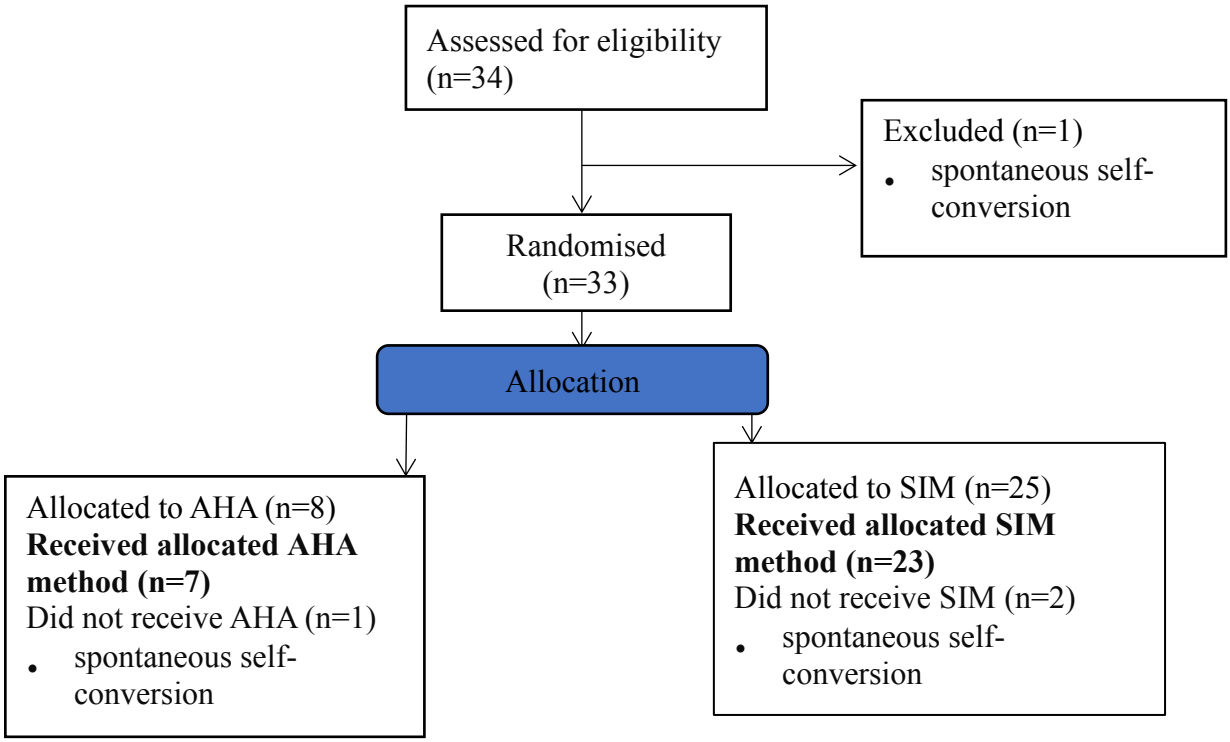

Fig 1 Patient enrolment, randomisation

Table □: Baseline demographic and clinical characteristics of participants

	SIM intervention n=23	**AHA intervention n=7**
Age years		
18-59	**16(39*)**	**5(39*)**
60-80	**7 (69*)**	**2(67*)**
Gender		
Male	**5 (21.7%)**	**2 (28.6%)**
Female	**18(78.3%)**	**5 (71.4%)**
Ethnic origin		
African	**13 (56.5%)**	**5 (71.4%)**
Asian	**9 (39.1%)**	**2 (28.6%)**
Colored	**1 (4%)**	**0**
Co-morbidity		
Chronic obstructive pulmonary disease	**2 (8.7%)**	**0**
Hypertension	**4 (17.4%)**	**3 (42.9%)**
Diabetes Mellitus	**3 (13%)**	**1 (14.2%)**
Ischemic heart disease	**1 (4%)**	**1 (14.2%)**
Bronchopneumonia	**3 (13%)**	**1 (14.2%)**
Valvular heart lesion	**0**	**1 (14.2%)**
Previous SVT	**6 (26%)**	**0**

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No previous SVT	**1 (4%)**	**1 (14.3%)**

***Mean age of the participants**

Table □: Successful outcome results

Dose success	SIM intervention n=23	AHA intervention n=7	P-values
1st dose conversion	13/23	4/7	0.9781
2nd dose conversion	4/23	1/7	0.847
3rd dose conversion	0	0	1
Total conversion rate:	17/23	5/7	0.897

Table □: Failed outcome results

SIM method n=6	AHA method n=2	P value	Relative Risk	95% one side CI
6/23	2/7	0.897	0.9130	-0.294; 0.344

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Authors contribution

Dr. Amanda Makhubela	50%
Prof Andreas Engelbrecht	45%
Dr. Suma Rajan	5%

Declaration of competing interest

The authors declared no competing interests