University of Pretoria
Faculty of Health Sciences
School of Medicine

Title: A randomised controlled trial of the standard versus a simplified adenosine administration method in the treatment of adult patients with supra-ventricular tachycardia (SVT)

Degree: MMed Emergency medicine

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14 February 2018

1. EXECUTIVE SUMMARY

Adenosine is a naturally occurring endogenous nucleoside which is frequently used as a first line therapy for patients experiencing an episode of supraventricular tachycardia (SVT). It works by suppressing the sinoatrial and atrioventricular nodal conduction time and thereby terminating re-entrant tachycardias. Adenosine undergoes rapid biotransformation and has a half-life of less than 10 seconds. Elimination occurs through cellular uptake in red blood cells and the vascular endothelium. Because of these characteristics adenosine has to be administered through rapid intravenous administration and must be followed by a bolus of saline. The current method of adenosine administration as suggested by the American Heart Association (AHA) and taught on advanced life support courses in South-Africa and elsewhere is cumbersome and frequently leads to maladministration by healthcare workers. The aim of this project is to test if a simplified method of rapid intravenous adenosine administration is not as effective as the AHA recommended method. Patients who present with an episode of re-entry SVT will be randomized into an intervention and control group. The intervention group will receive adenosine by a simplified method in which Adenosine will be combined with a saline flush. The control group will receive Adenosine via the standard recommended method by the AHA. The primary outcomes of this study will be the conversion rate to sinus rhythm in the intervention vs. control group. Side effect and complication rates in both groups will also be compared. The outcome of this study may lead to wider acceptance of a simplified and more elegant more convenient method of Adenosine administration and improved health care provider and patient satisfaction. It may further lead to a change in the current teaching on Adenosine administration in advanced life support courses.

2. INTRODUCTION

Supraventricular tachycardia (previously referred to as paroxysmal supraventricular tachycardia) due to various reentry mechanisms is a relatively common presentation to emergency departments. 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 the drug of choice given rapidly intravenously when the SVT does not respond to vagal maneuvers. The initial recommended dose for adult patients is 6mg over 1-3 seconds through a large vein, followed by a 20ml saline flush. Up to two follow up doses of 12mg each can be given if the arrhythmia fails to convert.[2]

The popular ring bound 2010 Handbook of Emergency Cardiovascular Care for Healthcare Providers of the American Heart Association® describe the technique of rapid intravenous administration of adenosine as follows:

Injection Technique.[3]

- Record rhythm strip during administration.
- Draw up adenosine dose (6 or 12mg) and flush (20ml Normal Saline) in 2 separate syringes.
- Attach both syringes to the IV injection port closest to patient.
- Clamp IV tubing above injection port.
- Push IV adenosine as quickly as possible (1-3 seconds)
- While maintaining pressure on the adenosine plunger, push NS flush as rapidly as possible after adenosine
- Unclamp IV tubing.

This technique requires training and co-ordination to be successful and problems arise when the adenosine, upon rapid injection enters the larger syringe with the saline flush instead of the vein of the patient; when the saline flush inadvertently enters the adenosine syringe; disconnection of the syringes resulting in fluids squirting outside the line and possibly into the eyes of healthcare providers or the patient. Such is the complexity that the Advanced Cardiac Life Support Instructors in South-Africa often recommend that a second person should assist to stabilize the syringe connections and also turning the three way stop connector.

The research question arises then that in adult patients with re-entry SVT is a simpler method of intravenous adenosine administration (intervention) not inferior to the AHA method (control) to achieve conversion to sinus rhythm (outcome)?

This study will compare a much simpler technique of rapid intravenous administration of adenosine with the above mentioned technique. The simplified technique entails combining the adenosine with the saline flush in a 20ml syringe given as a rapid bolus. Conversion rates to sinus rhythm and complication rates for the two techniques will be compared.

Adenosine has had significant electrophysiological effects on cardiac conduction since 1929.[4] In one animal study, adenosine produced atrioventricular block and sinus bradycardia in several mammalian species including dogs.[4] A calcium channel blocker, verapamil was the drug of choice for the treatment of SVT. However, adenosine has been shown to be as effective as verapamil, with fewer serious side effects, particularly hypotension.[5] The conversion rate in this trial was 93.4% for the Adenosine group and 90.6% for the verapamil group where patients were treated with up to two doses of their assigned drug. This difference was not statistically significant. Adenosine also had more rapid onset of action than verapamil and was eliminated much faster from the system. Verapamil has an elimination half-life of 4 to 8 hours.[22]

Adenosine was found to be safe in arrhythmias such as Wolff-Parkinson-White syndrome in which verapamil caused significant complications like ventricular fibrillation and cardiac arrest.[6] The American Heart Association has recommended adenosine as the first-line treatment for SVT in adult patient since the early 1990's.[7] It has also been shown to be safe in unstable patients with SVT, where instability was defined as patients with a blood pressure of less than 90 mm Hg, pulmonary edema, chest pain or an altered mental status.[8]

A Medline search using search terms including adenosine, supraventricular tachycardia, intravenous administration and dilution was performed, and articles relevant to this research project included a landmark study by DiMarco in which adenosine was compared with verapamil and with a placebo, adenosine doses were followed by a saline flush.[5] Neither the volume nor the method of administration of the flush are mentioned. In an earlier study by DiMarco a 10ml saline flush was used[9] and the results were ground breaking for the effectiveness of adenosine for SVT. Increasing doses of adenosine were assessed in 46 patients with SVT. Patients underwent electrophysiological studies to determine the mechanisms of arrhythmia. Sixteen patients had AV reciprocating with accessory pathways and all 16 converted on adenosine. Thirteen out of 13 patients with AV nodal reentry tachycardia also converted. Adenosine was not effective in patients with atrial fibrillation (AF), atrial flutter and intra-atrial reentrant tachycardia.

Varying volumes of saline were used in studies that investigated conversion rates for pre-hospital SVT using adenosine at 6, 12 and 18 mg as a rapid IV bolus given over 1 to 2 seconds followed by a 30ml saline flush.[10] Overall conversion rates improved from 32.4% to 59.1% after the introduction of adenosine.

The relatively low conversion rate in some studies was ascribed to the poor accuracy of ECG interpretation by paramedics despite additional educational measures. Adenosine was administered inappropriately in cases of atrial fibrillation, atrial flutter and ventricular arrhythmia. In spite of transient side effects such as shortness of breath, flushing and dizziness, no serious complications were noted in any patients irrespective of the arrhythmia treated.

The comparison of adenosine and verapamil in the pre-hospital setting over two periods was also studied[11]. Six milligram of adenosine, followed by 12mg after 1 to 2 minutes if the initial dose was unsuccessful in rhythm conversion was used followed by a 10ml saline flush. Findings were a 78% conversion rate (25 of 32 patients) compared to an 82% conversion rate for verapamil (9 out of 11 patients). In this study paramedics were under supervision of base hospital physicians who may have been reluctant to order verapamil because of its side effects and safety profile. This may have led to a low number of patients in the verapamil period of the trial. This study also showed that paramedics and base hospital physicians misdiagnosed the presenting arrhythmia in 30 of 73 cases (41%) compared with cardiologists. This study was further limited by the small sample size.

Another study compared the rate of recurrence of SVT in a group given oral Verapamil post successful conversion with intravenous adenosine to a group not given verapamil after adenosine converted SVT in the ED.[1] Verapamil is a calcium channel blocker that inhibits the influx of calcium proportionately to the plasma concentration. It has a half-life of 3 to 6 hours with insignificant amount of metabolites as well as elimination via extra-renal routes. It is used to control arrhythmias by decreasing SA nodal firing and slowing down AV nodal conducts.
In this study the recurrence of SVT was statistically significantly lower (p= 0.042) in the adenosine/verapamil group vs the adenosine only group between 30 and 120 minutes after treatment. Although in the rest of the follow up period there was no further recurrence was seen in the two groups.[1]

Another pre-hospital study by showed the safety and efficacy of intravenous adenosine for pre-hospital treatment for SVTs.[12] This study was a prospective case series carried out over a 10 month period. All patients with a pre-hospital field diagnosis of PSVT were included. Patients who were excluded were pregnant, younger than 14 years, older than 85 years of if they had a recent history of ingestion of dipyridamole or carbamazepine.

Adenosine was administered in doses of 6 mg followed by a flush of 5ml normal saline or ringers lactate. Two doses of 12 mg adenosine again followed by a 5ml flush of normal saline or ringers lactate were given with first failure to convert. Of the 41 patients included in the study 31 were correctly diagnosed. Most of the misdiagnosed cases had atrial fibrillation. Of the 31 cases correctly diagnosed as PSVT 28 converted to sinus rhythm after adenosine (90.3%). 16 (57.1%) required a single dose, 9 required one additional dose (32.1%) and three required two additional doses (10.8%). This study was interesting since it indicates that adenosine can be very effective (90.3% conversion rate) even when a much smaller saline flush is used than the 20ml flush that is recommended by the AHA.[3] No adverse effects were found in the patients who had atrial fibrillation who received adenosine. In fact it was found that the temporary AV block assisted in the diagnosis of AF. This study was limited by its design which lacked a control group and by the small sample size.

In the above mentioned studies, saline or ringers lactate flushes ranging from 5ml to 30ml were used after adenosine administration. We did not come across any studies were adenosine were administered without a saline or ringers lactate flush.

The inclusion and exclusion criteria for the three pre-hospital studies mentioned above are compared in table 1 below. These inclusion and exclusion criteria are significant to our study since it was made on clinical grounds similar to what we plan for our study. In the studies of DiMarco, electrophysiological measures were used which will not be feasible in our study.

Table 1: The inclusion and exclusion criteria table

Study:	**Conversion rates fo Pre-hospital PSVT with addition of ade nosine[10]**	**A comparison of ad nosine and verapar for treatment of SV in the prehospital setting[11]**	**IV adenosine as first line management of SVT without Physician control[12]**
Inclusion criteria:	Age 18 years or olde presumed diagnosis of PSVT by EMT PSVT definition: Regular narrow com- plex tachycardia be- tween 140 and 250 beats / minute.	Protocol for SVT: QRS duration less Than .12s and regu- lar rhythm. QRS rate between 160 and 240.	Did not respond to va- gal maneuvers. Regular narrow com- plex tachycardia. Rate equal to or grea- ter than 160/ minute
Exclusion criteria:	• Pregnancy • Taking carbamaz pine or dipyridamole • Known allergy to • adenosine.	• Systolic BP < 90 • Altered mental sta • Chest pain • Diaphoresis • Possible MI • The above patien • Received electric cardioversion if th met the ECG criteria	• Pregnancy • <14yrs; > 85yrs • Recent ingestion of Carbamazepine or d pyridamole. • Unstable patients as in the Madsen study • received electrical cardioversion.

Table 2: Co morbid conditions included in the studies

Study	Postural modification to the standard Valsalva manoeuvre for emergency treatment of supraventricular tachycardias (REVERT): a randomized controlled trial[23]	Oral verapamil in paroxysmal supraventricular tachycardia Recurrence control: a randomized clinical trial[24]
Co morbid conditions	• Prev SVT Dx • Prev SVT not Dx • Prev ablation Rx • COPD • Pneumonia • IHD • Diabetes • Hypertension • Valvular heart lesion	• Hypertension • IHD • Diabetes Mellitus • Obstructive lung disease

A number of studies and case presentations that related to the importance of the type of intravenous access needed for effective adenosine administration were found. Although an animal study on piglets showed that adenosine was effective when given through an intraosseous line[13], human case studies did not support this finding. Goodman and Lu[14] described two cases of infants that presented with SVT's refractory to vagal maneuvers. Intravenous placement was difficult in both cases and intraosseous access was achieved. Administration of adenosine in increasing doses did not convert the arrhythmias. In both cases the patient was referred for expert assistance. In the first case an IV line was obtained and the patient converted after one intravenous dose of adenosine followed by a saline flush. In the other case a central line was placed in the right femoral vein and again the patient's arrhythmia converted to sinus rhythm after a single dose of adenosine and flush. This suggested that the intraosseous route was not effective for adenosine administration.

In a case study described by Connor, the importance of the diameter of the intravenous cannula was highlited.[15] A 15-year old male patient presented with a SVT of 180 beats per minute. The patient reported having had similar previous episodes. The parents forewarned the emergency department doctor that high doses of adenosine were usually required for cardioversion and that the most recent episode required 18 mg. A large 18 G green cannula was inserted and 6 mg of adenosine was given followed by a 20 ml flush of normal saline. The patient experienced chest pain and breathlessness, which abated when sinus rhythm was restored within 10 seconds. The patient had never before experienced similar symptoms during adenosine administration. However, it became clear that yellow 24 G intravenous cannulae had been used on the previous occasions. This case suggested that smaller gauged cannulae do not facilitate sufficient flow rates and therefore necessitate repeated and higher dosages of adenosine.

Another study in McIntosh-Yellin[16] looked at peripheral vs. central administration of adenosine in 30 subjects. These patients underwent electrophysiological studies and received adenosine via the central and peripheral lines. Peripheral injections were given via an IV line in the upper extremity and central infusions were given through a catheter positioned in the right atrium. The site of administration was randomized and each subject received adenosine via both routes. Adenosine was administered in increasing increments of 3, 6, 9 and 12 mg until the tachycardia terminated. Responses to peripheral administration were compared with those centrally administered.

Tachycardia was terminated in 11 patients with 3 mg (37%), in 10 (33%) with 6 mg, in 4 (13%) with 9 mg and in 5 (17%) with 12 mg. In contrast, after central administration, 23 episodes of tachycardia (77%) were terminated with 3 mg, 6 (20%) with 6 mg and 1 (3%) with 9 mg; none required 12 mg. Lower doses of adenosine were needed with central administration. Sixty-three percent of the subjects required a lower dose. This study concluded that the initial dose for central administration of adenosine should be 3 mg. A case study that documented a severe prolonged (13s) episode of bradycardia in a patient that received 12 mg of adenosine via a central line was also found in the literature.[17] The patient also experienced severe agitation and chest pain. The AHA recommended that patients should receive an initial dose of 3 mg of adenosine when it is administered through a central line.[2]

We identified two studies that determined the stability of adenosine inside various diluents inside syringes and bags. Ketkar[18] compared the stability of adenosine in saline, ringers lactate and dextrose in polypropylene syringes and polyvinyl (PVC) bags at three temperatures. It was shown with high performance liquid chromatographic analysis that adenosine 3 mg / ml was stable in polypropelene syringes and PVC bags for 7days at 25 ºC, 14 days at 5 ºC, and 28 days at -15 ºC. Lower concentrations were stable for longer. Fungal growth was only found after many days (10 and 16) in dextrose solutions.

No fungal growth or change in liquid appearance was detected where adenosine was diluted in saline or ringers lactate. Adenosine was also found to be stable and compatible with saline by Kaltenbach.[19]

In the clinical experience of the researcher and colleagues in the field of emergency medicine, drawing up adenosine with the flush is as effective as using the AHA method of two syringes. By doing a web-search it was discovered that Bryan Hayes, Pharm D[20], advocated this simplified technique on Academic Life in Emergency Medicine (ALiEM) a well-known emergency medicine website. On this blog he motivates the simplified technique citing the following reasons why it is effective: “the major advantage to this approach is that it obviates the need for any syringe switching or stopcock swiveling. There’s no need for additional flushes since your diluted adenosine syringe doubles as the flush. If you don’t have 20 ml syringes, you can still add the adenosine to one of the two 10 ml saline flushes and get the same effect. Flush volumes as low as 5 ml have been effective.”

Only one study could be found in the literature that compared a simplified technique of adenosine administration with a “standard” technique. It is not clear if the standard technique refer to the technique described in the 2010 Handbook of Emergency Cardiovascular Care for Healthcare Providers of the American Heart Association®.

This study, which was published in Korean, is not well known since it is rather difficult to translate into English and therefore difficult to critically appraise .[21] From the English abstract of the article the following information was obtained. The purpose of the study was to observe the success rate, the average dose and the complications associated with a “convenient” method of adenosine administration for paroxysmal supraventricular tachycardia. A non-blinded, randomized, prospective study was conducted from January 1999 to June 2001. Sixty-five Cases were enrolled during this period. Thirty-five cases received adenosine by the standard method. The standard method is not described in the abstract and is not clear from a Google translation of the main text. Thirty cases received adenosine by a “convenient” method.

This method is described as a mixture of 6 mg adenosine in 15 ml of normal saline. The results from this study indicated that a success rate of 80% was achieved in the standard method group and 85.7% was achieved in the group that received adenosine via the “convenient” method. The difference was not statistically significant ($p = 0.39$). No significant complications were found in the patients who received adenosine via the “convenient” method.

Dipyridamole, carbamazepine, B-blockers, digoxin, verapamil and diltiazem may potentiate the action of adenosine while theophylline and caffeine antagonize the antiarrhythmic effects of adenosine.[2,22] Adenosine should not be used for irregularly irregular tachyarrhythmias, especially when the QRS complex is widened. This is because of the possibility of initiating atrial fibrillation with a very rapid ventricular rate in a patient with pre-excitation such as WPW.[2]

According the South African Medicines Formulary (SAMF), adenosine should only be given if cardiac monitoring and resuscitation is available.[22]

We hope that our study will clarify whether a simple technique of adenosine administration by mixing it with the flush solution is not inferior to the method described in the 2010 Handbook of Emergency Cardiovascular Care for Healthcare Providers of the American Heart Association®.

3. AIM AND OBJECTIVES:

Aim: To investigate if a simplified method of IV adenosine administration *is* not inferior to the standard AHA method of IV adenosine administration.

Objectives:
1) To determine the proportion of patients who converted to sinus rhythms in the simplified vs. the standard method of adenosine administration.

2) To determine the number of complications in the simplified vs. the standard method of adenosine administration.

3) To determine the types of side effects in the simplified vs. the standard group of adenosine administration.

4) To determine the time to conversion to a sinus rhythms in the simplified vs. the standard method of adenosine administration.

Hypothesis: Our hypothesis is that the simplified method of IV adenosine administration is not inferior to the standard AHA method of IV adenosine administration.

H_0 (Null Hypothesis): A simplified method of IV adenosine administration is inferior to the standard AHA method of IV adenosine administration.

H_1 (Research Hypothesis): A simplified method of IV adenosine administration is not inferior to the standard AHA method of IV adenosine administration.

4. METHODS

In our study a simplified method of adenosine administration will be compared to the standard AHA recommendation. This will be a non-inferiority study.

4.1. STUDY DESIGN

Prospective, non-blinded, non-inferiority, randomized controlled trial.

4.2. SETTING

Two Tertiary academic hospitals (Steve Biko Academic Hospital and Kalafong Academic Hospital) will be used for the study, as well as two Life private hospitals (Eugene Marais and Wilgers Hospital). Patients presenting to the emergency departments (ED's) and admitted to the cardiology / internal medicine wards will be included.

4.3. PATIENT SELECTION

Sampling strategy: Due to the relatively scarce nature of SVT in adult patients with an estimated incidence of 1 case per week per institution all new cases of SVT that meets the inclusion criteria will be included in the study. Patients may be included in the trial more than once if they have a repeat episode of re-entry SVT more than four hours after return to sinus rhythm.

Inclusion criteria:

- All EKGs must have been sent via whatsapp messenger to Prof Engelbrecht to validate SVT before inclusion
- Age: 18 years to 85 years.
- Presumed diagnosis of re-entry SVT.
- Re-entry SVT not responsive to two valsalva attempts lasting 15 to 30 seconds.

Definition of suspected re-entry SVT:
The spontaneous onset of a regular narrow complex (QRS duration less than 0.12s) tachycardia greater than 150 and up to 240 beats per minute.

Exclusion criteria:

- Patients who are clinically too unstable to give consent:
  - Impaired consciousness
  - Significant chest pain, shortness of breath or pulmonary oedema
  - Systolic blood-pressure below 90mmHg

- ECG features:
  - QRS width more than 0.12 seconds (3 blocks on ECG paper)
  - R-R interval irregular
- Known allergy to adenosine
- Recent ingestion of dipyridamole, carbamazepine or theophylline.
- Ingestion of caffeine in the previous 2 hours.
- Acute asthma attack
- Heart transplant
- Patients who were already included in the trial who suffer a second episode of re-entry tachycardia less than 4 hours after the first episode.

Randomization procedure:
To increase the power of the study for the anticipated low numbers of patients, a 2:1 randomization procedure of the simplified vs. the standard procedure will be followed.
10 envelopes will be randomized at a time into research and control groups for the four participating sites to be used by the principal investigator. These envelopes will be containing instructions on either of the two administration methods.

For each of the four sites, one third of the prepared envelopes will contain instructions on the standard AHA method of IV adenosine administration and the remaining two thirds will contain instructions on the simplified method of IV adenosine administration.

These envelopes will be sealed and will have no external indication of which method is described inside. The sealed envelopes will then be thoroughly shuffled and thereafter numbered from 1 to 10 at a time. Each new patient enrolled will receive the next number. Numbers may not be skipped.

Treatment will be administered by medical officers and registrars from the emergency department of Steve Biko and Kalafong Hospitals; by registrars from the department internal medicine at Steve Biko and Kalafong Hospitals; or by the ED doctor on duty at the two Life private hospitals (Eugene Marais and Wilgers Hospitals). Only doctors who received training on the protocol by the principal investigator will be allowed to enrol patients and administer the treatment. Training sessions will be organized by the principal investigator at Steve Biko and Kalafong hospital prior to the enrolment of the first patient.

The treating medical practitioner of patients who agree to participate in this trial will receive a randomized envelope. He will administer adenosine according to the instruction given inside the envelope and document demographic data as well as the conversion rate to sinus or other rhythms as well as any side effects or complications on a case report form (CRF), which will also be in the envelope. The CRF and informed consent will then be collected by the investigator.

4.4. MEASUREMENTS

For each patient the ECG rhythm of standard lead II will be monitored continuously with a monitor-defibrillator throughout the management of the patient. An ECG rhythm strip will be printed for at least 15 seconds before and 1 minute after each adenosine administration.[2]

Outcome measurements:

A successful outcome will be defined as an ECG rhythm conversion from re-entry SVT to sinus rhythm for at least 10 minutes. Sinus rhythm will be defined as regular ECG rhythm in standard lead II of between 60 and 100 beats per minute where each p-wave is followed up by a QRS complex.

A failed outcome will be defined as a persistent re-entry SVT or conversion to an alternative arrhythmia that requires rescue therapy after up to three doses of Adenosine.

Outcomes will be adjudicated by the treating clinicians who will receive training on the protocol of the trail including ECG analysis. Post hoc analysis will be done by the investigators.

Conversion rate to sinus rhythm will be determined for each technique. The number of doses needed per case will be recorded.

Additional measurements:

The initial heart rate and the systolic blood pressure will be recorded. These measurements will be repeated 1 to 2 minutes after each dose of adenosine is administered.

The heart rate and systolic blood pressure will be measured with electronic blood pressure devices. These measurements will be taken irrespective of whether rhythm change took place or not.

Side effects or complications will be documented.

Safety and monitoring:

Several trials have demonstrated that Adenosine is safe and effective in the treatment of reentry SVT.[5,8-12] As a safety method, all EKGs will be sent via whatsapp messenger to Prof Engelbrecht to validate the SVT before inclusion into the study who is an expert in EKG interpretations.

Adenosine should not be used for irregularly irregular tachyarrhythmias, especially when the QRS complex is widened. This is because of the possibility of initiating atrial fibrillation with a very rapid ventricular rate in a patient with pre-excitation such as WPW.[2]

All clinicians who will enroll patients on this trial will be trained on ECG assessment and on how to exclude irregular and wide complex tachycardias.

Measurement of the width of the QRS complex and an assessment of the regularity of the R-R intervals will be documented in the clinical notes. Patients with a widened QRS complex (ORS width more than 0.12 ms) or an irregular rhythm R-R interval will be excluded.

Although life threatening arrhythmias are extremely rare after adenosine administration, the availability of a defibrillator is an essential component of this trial. The defibrillator will be checked prior to adenosine administration. The defibrillator check will be documented in the CRF.

Failed conversion:

Patients who do not convert to sinus rhythm after three doses of Adenosine or convert to a rhythm other than sinus rhythm will be treated with rescue therapy according to standard medical guidelines. These treatments may include electrical cardioversion, alternative drug therapy, hospital admission or referral to a specialist cardiologist.

4.5. DATA management and ANALYSIS

4.5.1. Statistical considerations

This non-inferiority study assesses standard versus simplified adenosine administration in the treatment of adult supraventricular tachycardia patients.

Data will be captured on a paper based data capturing sheet called a case record form (CRF). From this form the data will be transferred on to an excel spread sheet from which statistical analysis will be performed. Result will be illustrated with tables and grafts.

4.5.2. Sample size

The following assumptions was made in calculating the sample size: a response rate of 0.9 for both methods, a noninferiority delta = -0.12 (-12 %) and a 95% one sided interval. Randomisation will be 2:1 for the simplified administration method vs. the standard method. A sample of 94 and 47 patients (a total of N=151) for the two arms of the study respecitvely will be feasible due to the low frequency of the condition. This sample size wil result in a power of 80.3% in this study. If the recruitment rate is higher than expected, extention of the study to enroll more patients, will be considered to further improve the power.

4.5.3. Data analysis

A 90 % two sided confidence interval will be determined for the difference between simplified and standard response rates. Should the lower limit of this 95% one sided confidence interval (90 % two sided) exceed -0.12 the simplified method will be regarded as non-inferior to the standard method. However, should it also be in excess of 0, the simplified method will be superior to the standard method.

5. ETHICAL CONSIDERATIONS

Informed consent will be obtained from all patients who participate in this trial.
Consent will be obtained from the relevant heads of departments and CEO's of the hospitals to allow enrollment of patients at each of the facilities.
An application will be made to the Ethics Committee of the University of Pretoria for approval of the protocol.
This trial will be registered as a clinical trial at clinical trials.gov.
The Medicines control council (MCC) will be notified of this trial.

The CRF's and any additional paper based or electronic data from this trial will be stored at Steve Biko Academic hospital in room 72441 for 10 years. All paper based and electronic data will be kept strictly anonymous. No non-clinical personal detail, names or hospital numbers will be recorded in the CRF or in any other electronic or paper based document.

6. BUDGET

1. All costs for medications and consumables are part of standard medical care that patients would have received irrespective of the trial.

2. A honorarium of R150 will be paid to each clinician who enrolls a patient on this trail. A budget of R7500 for this purpose will be obtained from the Emergency Medicine Research Fund. This will provide payment for 50 enrollments. The deficit will be enrolled by the investigators and without payment.
3. All additional costs will be covered by the researcher (± R500 for stationary).

4. Total cost: ± R 8000.

7. TIME LINES AND PROJECT MANAGEMENT

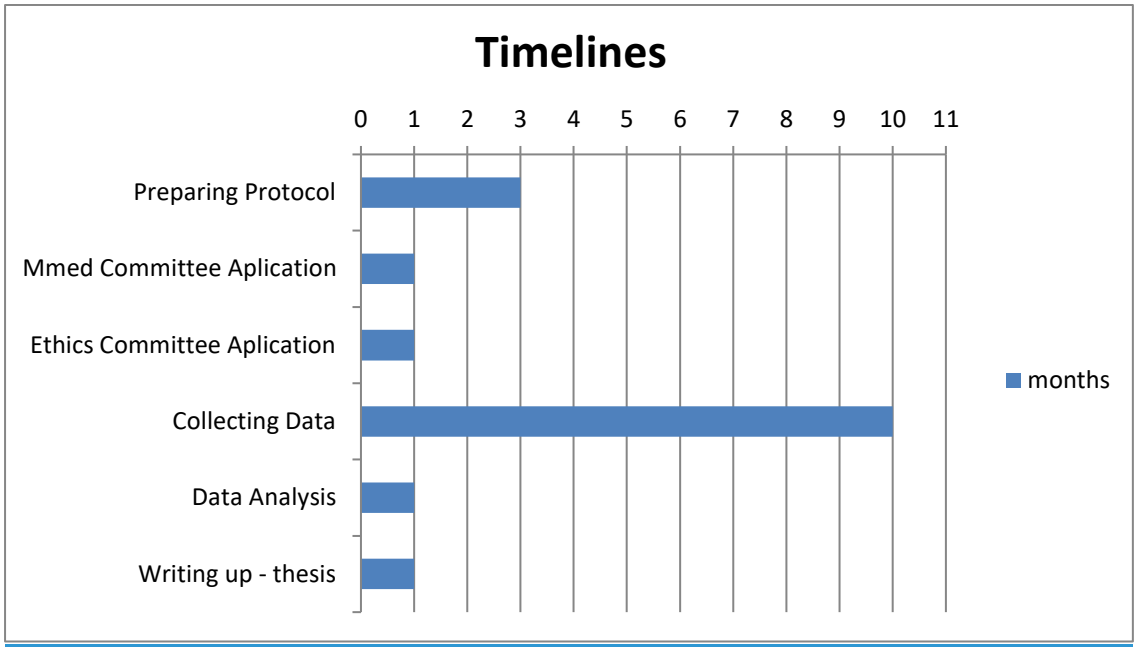

Figure 1- The gannt chart

Dates:

	Date:
Preparing Protocol	3 Dec ‘17
Mmed Committee Application	15 Mar ‘18
Ethics Committee Application	15 Apr ‘18
Collecting Data	15 May '18
Data Analysis	1 Jan '19
Writing up – thesis	1 Feb '19

8. CONTRIBUTORS AND AUTHORSHIP (leader and follower)

Name	Department	Contribution	Author or acknowledgement
Dr. Amanda Makhubela	Emergency Medicine	Researcher / Main Author	Author
Prof. Andreas Engelbrecht	Department of Family Medicine / Division of Emergency Medicine	Researcher / Main Author	Co Author

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