A SURVEY ON THE USE OF VASOPRESSOR AND INOTROPIC AGENTS OVER THREE MONTHSAT THE KENYATTA NATIONAL HOSPITAL

DISSERTATIONSUBMITTED IN PART FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN ANAESTHESIA OF THE UNIVERSITY OF NAIROBI

Principal investigator:

Simiyu Victoria M., MBChB (UoN)

DECLARATION

Principal investigator:

I hereby declare that this dissertation is my original work and that it has not been submitted to any university or institution for examination or any other purposes.

Signed _____Date _____

Simiyu V.M., MBChB (UoN)

Post-graduate student in Anaesthesia

University of Nairobi registration number: H58/68385/2011

Supervisors:

This dissertation has been submitted for the degree of masters of medicine in anaesthesiology with my approval as a university supervisor.

Signed _____Date _____

Dr. J.M.Muriithi,

MBChB , MMed Anaesthesia (UoN)

Lecturer in Anaesthesiology; Department of Anaesthesia, UoN.

Signed _____Date _____

Dr. S. Nabulindo,

MBChB, MMed Anaesthesia (UoN)

Lecturer in Anaesthesiology; Department of Anaesthesia UoN.

TABLE OF CONTENTS

ABSTRACT

Background

In Kenyatta National Hospital vasopressor and inotropic agents are used in specialized units-CCU and HDU. Knowledge of the varied pharmacology and mechanism of action of the agents allows for proper selection and thus desired outcome. This is done by medical staff with appropriate experience and training. These drugs are known to impact on patient outcome though guidelines are not readily available to give guidance on management and allow for standardization of treatment. Therefore individual experience and preference determines selection.

Objective

To survey the use of vasopressor and inotropic agents over three months at KNH.

Study design

An observational, descriptive study.

Setting

Kenyatta National Hospital-Critical care unit, emergency ward, high dependency units. It was carried out over three months from approval of the study.

Study population

Patients admitted in the above units on inotrope or vasopressor agent that was initiated at KNH.

Sample size

The sample size was determined by the modified Fisher's formula:

=**70**

Sampling procedure

Convenient sampling was used to select the patients. The eligible patients were recruited consecutively into the study using the inclusion criteria

Inclusion criteria;

- Patients in main CCU and Emergency ward on inotropic/vasopressor agent initiated at KNH.
- Patients whogave consent to participate in the study.

Exclusion criteria;

- Patients who didn't consent to participate in the study.
- Patients transferred to KNH who were already on inotropic or vasopressor therapy.

Study variables

These included identifying the types of inotropic/vasopressor agents available, document their indications, modes of haemodynamic monitoring and the techniques used to administer the agents.

Data management and analysis

Data was presented as numbers (%) or mean ± SD and summarized using tables, histograms and pie-charts as appropriate. Descriptive and inferential statistics were used to analyze the data.

All analyses were performed using SPSS (statistical package for the social sciences) Statistics (version 20, Chicago, IL).

Results

Data from 70 patients were collected and recorded. 94% were adult patients. 59% of the patients were female. The leading cause for initiating inotropes was septic shock (48.6%). The inotropes that are available for use were dopamine, norepinephrine, epinephrine and dobutamine in order of most prescribed agent. In patients with septic shock norepinephrine and dopamine were the inotropes of choice while in cardiogenic shock epinephrine and dobutamine were the inotropes of choice. 97% of the time inotropes were initiated on the same day. The mode of haemodynamic monitoring commonly used is basic monitoring (defined in this study as heart rate, pulse oximeter, central venous pressure and non-invasive blood pressure). Through the study quick change was used in substituting inotrope infusion. Infusion pumps were used to administer the agents 100% of the time.

Conclusion

The use of inotropes/vasopressors at the Kenyatta National Hospital is fairly well executed in the critical care areas.

LIST OF ABBREVIATONS

ACC	American College of Cardiology
AHA	American heart association
BP	Blood pressure
CABG	Coronary artery bypass graft
CCU	Critical Care Unit
CO	Cardiac output
CVP	Central venous pressure
ECG	Electrocardiograph
HDU	High dependency Unit
KNH	Kenyatta National Hospital
MAP	Mean Arterial Pressure
SHO	Senior House Officer
SOAP	Sepsis occurrence in the acutely ill patients
SV	Stroke volume
SVR	Systemic vascular resistance
UCI	University of California Irvine

OPERATIONALDEFINITIONS

Basic monitoring refers to minimal expected monitoring. This includes ECG, non-invasive BP, heart rate, central venous pressure

Advanced monitoring refers to superior modes of monitoring that can be in addition to the basic monitoring. Invasive BP in an example.

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

The Kenyatta National Hospital is a referral hospital and the teaching hospital of the University of Nairobi. The hospital receives many patients who in the course of their treatment require inotropes and vasopressor agents. These agents are known to be life saving when initiated in good time and appropriately thus improving outcome, morbidity and mortality.

Vasopressors are class of drugs that elevate Mean Arterial Pressure (MAP) by inducing vasoconstriction whileinotropes increase cardiac contractility.These drugs have both vasopressor and inotropic effects.

Vasopressors are indicated for a decrease of >30 mmHg from baseline systolic blood pressure or MAP <60 mmHg, when either condition results in end-organ dysfunction secondary to hypoperfusion. In the paediatric age group MAP varies in with age. Therefore need of inotropes will be based on individual patients and clinical presentation.

They are highly potent drugs that should be administered by medical staff with appropriate experience and training. These drugs are usually administered by anaesthesia practitioners who also manage the critically ill patients in KNH. This may be in operating theatres or in a critical care unit set-up. They may also be called upon to give advice on the use of these agents in the medical wards and high dependency units.

The anaesthesia practitioners who also manage critically ill patients in KNH include:

- Anaesthesiologists

- Anaesthesiologists in training (SHO)

Intensivists are clinicians who may also prescribe inotropes. An intensivist is a physician who specializes in the care and management of patients in the intensive care. They from different medical specialities. In KNH the intensivists include internal medicine physicians, paediatricians and anaesthesiologists.

The critically ill patients at the KNH are found in the following units: critical care unit, emergency ward in casualty, high dependency units-cardiac and neurosurgery. This study is aimed at assessing the use of inotropic and vasopressor agents in the mentioned areas and be able to describe the agents available, indications and the monitoring that is used, through an observational study with a questionnaire as the data collection tool. A similar study has not been carried out at KNH.

LITERATURE REVIEW

Historical background

Dopamine was released in 1974 for use as an inotrope. Dopamine is one of the most complex and often misunderstood inotropic agents. The pharmacodynamic and haemodynamic effects are based on the dose administered. At low doses dopamine enhancesperfusion of vital organs and athigher doses is a vasopressor (1).

Dobutamine is a synthetic analog of dopamine. It was released in 1978 and was designed to be a selective inotropic agent based on Ahlmquist's theories of adrenergic stimulation. It was later found to have peripheral vascular activity (1).

Extracts of the adrenal glanddate as far back as 1895 discovered byNapoleon Cybulski while Japanese chemist Jokichi Takamine and his assistant Keizo Uenaka independently discovered adrenaline in 1900. Four years later it was synthesized in the laboratory byFriedrich Stolz andHenry Drysdale Dakin(2).

Use of inotropic and vasopressor agents in the management of patients with shock has increased.They are generally administered to improve cardiac output (CO) or vascular tone that has been severely compromised by often life-threatening clinical conditions. These agents are indicated for a decrease of >30mmHg from baseline systolic blood pressure or MAP <60mmHg when either result in end organ dysfunction due to hypoperfusion (3).

Receptor physiology

The categories of adrenergic receptors relevant to vasopressor activityarealpha-1adrenergic receptor, beta-1, beta-2 adrenergic receptors and dopamine receptors.Actions of these drugs on receptors influence the cardiac output and mean arterial pressure. Cardiac output is the product of heart rate and stroke volume while mean arterial pressure is the product of cardiac output and peripheral resistance.

Terms that are commonly used in describing the drug effects are inotropy, Chronotropy and vasoconstriction.Inotropy refers to drugs that alter the force of cardiac muscle contraction while chronotropy drugs that cause change of the heart rate by affecting the nerves controlling the heart or by changing the rhythm produced by the sino-atrial node.Vasoconstriction is the narrowing of the blood vessels resulting from contraction of the muscular wall to decrease in the caliber of the blood vessel.

The relative vasopressor activity of the common inotropes and vasopressor agents is dependent on receptor activity as summarized by figure1 and table 1.

AlphaActivity

norepinephrine = epinephrine>dopamine >phenylephrine

Strongest ← Weakest →

Beta Activity

epinephrine >dopamine>norepinephrine

Figure 1

Receptor Physiology

Receptor		**Location**	**Effect**
Alpha-1 Adrenergic		Vascular wall	Vasoconstriction
		Heart	Increase duration of contraction without increased chronotropy
Beta Adrenergic	**Beta-1**	Heart	↑Inotropy and chronotropy
	Beta-2	Blood vessels	Vasodilation
Dopamine		Renal Splanchnic (mesenteric) Coronary Cerebral	Vasodilation
	Subtype		Vasoconstriction

Table 1

REVIEW OF THE PHARMACOLOGY AND INDICATIONS OF THE AGENTS

Inotropes are used to manipulate critically ill patients' physiology, to maintain tissue perfusion and prevent end organ damage. At the point where patients are adequately resuscitated yet remain hypotensive the initiation of vasopressors may be required to achieve the desired MAP. Selection of a vasopressor is determined by the cause of shock and the desired therapeutic activity targeting the underlying pathogenesis.This is summarized on table 2.

Clinical Application

		1st Line Agent	2nd Line Agent
Septic Shock		Norepinephrine Dopamine	Vasopressin Epinephrine
Heart Failure		Dopamine Dobutamine	Milrinone
Cardiogenic Shock		Norepinephrine Dobutamine	
Anaphylactic Shock		Epinephrine	Vasopressin
Neurogenic Shock		Phenylephrine	
Hypotension	Anesthesia-induced	Phenylephrine	
	Following CABG	Epinephrine	

Table 2

SEPTIC SHOCK

Currently norepinephrine and dopamine are the first line vasopressors in septic shock management (4).A comparison study by SOAP II showed no significant difference between mortality rate between patients with shock on dopamine as first line or norepinephrine;

dopamine was found tohave more adverse events (5). Epinephrine should be the next alternative in septic shock resistant to norepinephrine or dopamine. Martin et al did a study identifying factors associated with outcome in septic shock. Norepinephrine was found to be strongly related to favourable outcome resulting in decreased mortality(6).

Dopamine

At low doses (0.5 to 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$), stimulation of dopaminergic D_1receptors and D_2receptors present in the vasculature and renal tissues promotes vasodilation and increased blood flow to these tissues. At intermediate doses (3 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), dopamine weakly binds to β_1-adrenergic receptors, promoting norepinephrine release and inhibiting reuptake in presynaptic sympathetic nerve terminals, which results in increased cardiac contractility and chronotropy, with a mild increase in SVR. At higher infusion rates (10 to 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$), α_1-adrenergic receptor–mediated vasoconstriction dominates.

Norepinephrine

Norepinephrine is a potent α_1-adrenergic receptor agonist with modest β-agonist activity, which renders it a powerful vasoconstrictor with less potent direct inotropic properties. This agent has minimal chronotropic effects, which makes it attractive for use in settings in which heart rate stimulation may be undesirable.

Vasopressin

It exerts its circulatory effects through V_1 (V_{1a} in vascular smooth muscle, V_{1b} in the pituitary gland) and V_2 receptors (renal collecting duct system). V_{1a} stimulation mediates constriction of vascular smooth muscle.

A vasopressin-modulated increase in vascular sensitivity to norepinephrine augments its pressor effects. The pressor effects of vasopressin are relatively preserved during hypoxic and acidotic conditions, which commonly develop during shock of any origin. Evidence suggests that low dose (<0.04U/min) is safe and effective for the treatment of vasodilatory shock (7)

Epinephrine

Epinephrine has high affinity for β_1-, β_2-, and α_1-receptors present in cardiac and vascular smooth muscle. β-Adrenergic effects are more pronounced at low doses(1-4 mcg/min) and α_1-adrenergic effects at higher doses (>10mcg/min).

CARDIOGENIC SHOCK

The ACC/AHA guidelines for ST-elevation myocardial infarction (STEMI) recommend the selection of vasopressor and/or inotrope therapy based on SBP plus the presence or absence of signs and symptoms of shock(8).

For patients with a SBP of 70-100 mmHg, dobutamine is recommended in the absence of shock and dopamine if shock is present. Norepinephrine is recommended when SBP is < 70 mmHg (8).

In a French multi centre survey the commonest used inotropes weredobutamine (65%) , norepinephrine (31%) and epinephrine (24%) in the management of low cardiac output syndrome (LCOS) (9).

In Germany in the management of LCOS epinephrine (41.8%) was found to be the commonest. Followed by dobutamine (30.9%) and phosphodiesterase inhibitors (14.8%) (10).

Dobutamine

Dobutamine has a strong affinity for both β_1- and β_2-receptors (3:1 ratio). At lower doses ($\leq$5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) causes mild vasodilation while at high doses up to 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increases cardiac contractility without greatly affecting peripheral resistance. Vasoconstriction dominates at higher infusion rates.

Dobutamine increases myocardial oxygen consumption. This property is applied in diagnostic perfusion imaging; but conversely, limits its use in clinical conditions in which induction of ischemia is potentially harmful. Ventricular arrhythmias are not dose dependant and tolerance develops within days of therapy (11).

Norepinephrine

Increases diastolic pressure that inturn improves coronary flow. The coronary flow is further improved by local vasodilators from the myocytes. Prolonged use has direct toxic effects on myocytes.

Epinephrine

Improves coronary blood flow by increased duration of diastole and release of local vasodilators. High doses and prolonged use damages arterial walls.

NEUROGENIC SHOCK

In acute spinal cord injury patients may present in neurogenic shock. Studies have shown improved neurological outcome associated with aggressive management and maintenance of a target MAP of 85-90mmHg.

Phenylephrine

It's the preferred vasopressor in neurogenic shock and hypotension as it has potent α-adrenergic activity and no affinity for β-adrenergic receptors. it's used as a rapid bolus to correct sudden severe hypotension.

HYPOVOLAEMIC SHOCK

Haemorrhageprogressingtohaemorrhagicshock,isthe leadingcauseofpreventabledeathin trauma (12). There isnowell-definedmeanarterialpressure (MAP)goalforpatientswithhemorrhagic shock. Early initiation of vasopressor within 24hrs in poorly resuscitated patients has been associated with increased mortality (13). Themainstayoftherapy isdamagecontrolresuscitation, which focusesonamassive transfusionofequal ratiosofpacked red bloodcellstofreshfrozenplasmatoplatelets plus surgical intervention (14).

Generally, inotropes have been shown to improve post-operative morbidity and mortality (15). This was achieved through balancing the beneficial effects of increased cardiac output against increased myocardial oxygen demand with inotrope use.

A practice survey on vasopressor and inotropic drug therapy in Scandinavian intensive care units concluded that dopamine (47%) and noradrenaline (40%) were the most

commonly used agents. Indications for inotropic/vasopressor use were hypotension (92%) and oliguria (50%). 32% used more than one drug (16).

In a French multicentre survey on the use of inotropes after cardiac surgery it was found that a single inotrope was used in 64% of cases, two inotropes in 26%, and three in 6%. Dobutamine was administered to 334 patients (65%). norepinephrine was the second most commonly chosen inotrope (157 patients [31%]), followed by epinephrine (24%) (17).

ADMINISTRATION AND MONITORING

Basic hemodynamic monitoring that is required while on inotropes/vasopressors includescontinuous ECG and BP monitoring. This is because these drugs have a short half life and overdoses can be life threatening. Central venous pressure and central venous saturationare additional parameters that should be monitored. In paediatrics central venous saturation may be used, with a target aim of >70% (18). It should be administered by nursing and medical staff with appropriate experience and training. Preparation and checking of calculations, dosages and dilutions should be done by two members of staff. This ensures mistakes are avoided.

Most agents must be administered through a central vein, although dobutamine is generally well tolerated via a peripheral vein.The2002 guidelines on paediatric and neonatal septic shockrecommended notgivingcardiovascularagentsuntil central vascularaccesswas attained.Thiswas because therewasandstillisconcernthatadministration ofperipheral vasoactiveagents (especiallyvasopressors) couldresult inperipheralvascular/tissueinjury. However, after implementationofthe 2002 guidelines,theliteratureshowedthat,dependingonavailabilityofskilledpersonnel,itcouldtaketwo

ormorehours toestablishcentralaccess. Because mortalitywentupwithdelayintimetoinotrope drug use,the 2007update nowrecommends use ofperipheral inotropes (not vasopressors) until central accessisattained(19).Continuous controlled infusions with horizontal syringes are used to administer the inotrope/vasopressor.

Error in labellingisa recognisedriskinthesafe administrationofinjectablemedicines. All areas of label should be completed.Placelabelsothattextisuprightandensurethattheburettegraduationsarenotobscured.The dateandtimethatthelineisrequiredtobechangedmustbeidentified.The line should be labeled twice.

There are two methods of substituting the infusion of inotropes through intravenous pump quick change (QC) and double pumping (DP). Quick change is whereby the empty syringe is changed as fast as possible with a ready filled syringe while double pumping uses two pumps at the same time to ensure no break in the infusion of the agents. Quick change was the quickest and most cost-effective(20). Infusions expire after 24hr and when changing ensure infusion line is clamped as the syringe is loaded into the driver, as the agent may be administered during the process.

STUDY OBJECTIVES

GENERAL OBJECTIVE

To assess the practice of inotropic and vasopressor therapy in the critically ill patients at KNH.

SPECIFIC OBJECTIVES

1. To identify the types of inotropic and vasopressor agents available.
2. To documentindications of use of the inotropic and vasopressor therapy.
3. To evaluate modes of haemodynamic monitoring.
4. To assess the technique of administration of inotropic and vasopressor therapy.

STUDY JUSTIFICATION

This research was intended to assess the useof inotropes and vasopressor agents at KNH. Inotropic/vasopressor agents are regularly used at the Kenyatta National Hospital though data to show the extent and pattern of use is not available. This is because such a study has not yet been done. These vasoactive agents are lifesaving and highlypotent as they cause minute by minute change. This study will allow KNH to have data on the common indications of these agents and to be aware of the commonest used agents. This allows for planning and appropriate stocking of the hospital units that often use these agents.

There are currently no guidelines available on the use of inotropes and vasopressors. This study will assist in the formation of guidelines that will be pivotal in improving patient care in the referral hospital. Guidelines allow for standardization of care that greatly improves quality of care.

RESEARCH METHODOLOGY

Study Design

A prospective -observational study.

Study Site

The study was conducted at the Kenyatta National Hospital main Critical Care Unit and the Emergency ward and the High Dependency units.

Study population

Patients admitted in KNH main CCU, High Dependency Units and Emergency ward initiated on inotropic/vasopressor agents.

Sample size

The sample size was determined by the formula:

$$n = \frac{t^2 \times p(1-p)}{m^2}$$

Description:

n = required sample size

t = the standard normal deviation at the required confidencelevel (in this case 1.96)

p = is the proportion in the target population estimated to have characteristics being measured. Since there is no estimate available of the proportion in the target population assumed to have the characteristics of interest, 50 %(0.5) as recommended by Fisher et al

(19).

m = level of statistical significance set= 0.05

Thus, n = $\frac{1.96 \times 1.96 \times 0.5(1 - 0.5)}{0.05 \times 0.05}$

n = 384

since the study population in this study was less than 10000, the sample size was calculated as follows:

nf= n/1+n/N

nf=the desired sample size (when the population is less than 10,000)

n=the desired sample size (when the population is more than 10,000) which is 384(as calculated above)

N=the estimate of the population size (estimated number of patients on inotropic/vasopressor therapy in KNH in a year)

Thus

Nf=384/1+(384/96)

=70

Sampling procedure

The study population was obtained from KNH-CCU, HDU and Emergency wardpatients whowere initiated on inotropic support. Convenient sampling was used to select the patients. The eligible patients were recruited consecutively into the study using the inclusion criteria below.

Inclusion criteria;

- Patients in main CCU and Emergency ward initiated on inotropic/vasopressor agent.
- Patients who consented to participate in the study.

Exclusion criteria;

- Patients who did not consent to participate in the study.
- Patients transferred to KNH who were already on inotropic or vasopressor therapy.

Data collection procedure

The eligible patients or their next of kin for those unable to give consent were required to give informed consent and complete a consent form before being involved in the study. The consenting process involved explaining to the patients or their next of kin the aim of the study, confidentiality and the use of the results. This was by the primary investigator. This took approximately ten minutes to ensure the patient or the next of kin had understood the content of the informed consent form. The presence of a witness (the primary nurse) was to ensure that the consenting procedure was done well and no relevant information was withheld. The primary nurse was the nurse allocated to care for the patient. The consent was administered at the point at which the decision to initiate inotropes was made.One copy of the consent was placed in the patients file and one copy retained by the primary investigator. The

consent copy with the investigator will be retained for a maximum of seven years.The data was collected using a questionnaire which was filled by the investigator. The information was from the medical records.

The investigator may have needed to interview the primary clinician in the unit to clarify but not to add to the information from the medical records. This was for the purposes of data quality control. The primary clinician was the SHO covering the floor at the mentioned study areas involved in the day to day patient care. Once data had been collected from the patient's file a yellow sticker was put on the cover of every file to avoid double recruitment.

Data Management and analysis

Data was presented as numbers (%) or mean ± SD and summarized using tables, histograms and pie-charts as appropriate. Descriptive and inferential statistics was used to analyze the data.

All analyses were performed using SPSS (statistical package for the social sciences) Statistics (version 20, Chicago, IL).

Data analysis plan

DUMMY TABLES

TABLE 1: socio-demographic characteristics

variable	**Frequency (%)**
Age(yrs)	

<10 **11-40** **>41**	
Gender Male female	

TABLE 2: indications for vasopressor/inotropic agent

variable	**Frequency (%)**
Septic shock	
Cardiogenic shock	
Anaphylactic shock	
Neurogenic shock	

TABLE 3: Inotrope/vasopressor choice

Drug	**1st**	**2nd**	**3rd**
Dobutamine			
Dopamine			

Epinephrine			
Isopreterenol			
Norepinephrine			
Phenylephrine			
vasopressin			

TABLE 4: Number of inotropes used

Number of inotropes used	**Frequencies (%)**
1	
2	
3	

TABLE 5: mode of monitoring

Mode of monitoring	**Frequency (%)**
Basic	
advanced	

TABLE 6: Mode of administration

Mode	**Frequency (%)**
Infusion pump	
other	

Ethical considerations

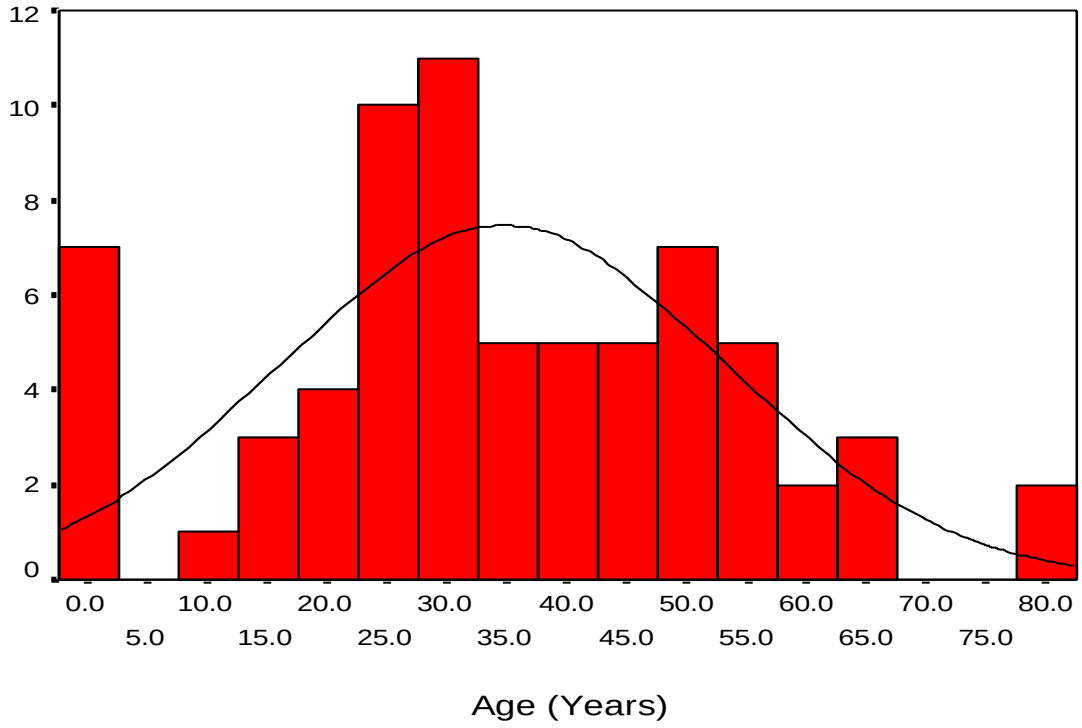
During the study the following ethical issues were considered:

1. No names of patients or practitioners were used in this study.
2. The study had no harmful effects on subjects. No extra costs were incurred by study subjects.
3. Treatment was notwithheld from those who declined to participate in the study.
4. Permission to conduct the study was sought from the Kenyatta National Hospital/University of Nairobi – Ethics & Research Committee prior to commencement.
5. Study findings will be shared with the ethics body as well as University of Nairobi, to facilitate appropriate policy formulation aimed at improving patient care.
6. Deficits found were discussed with the primary team and appropriate action was taken.

RESULTS

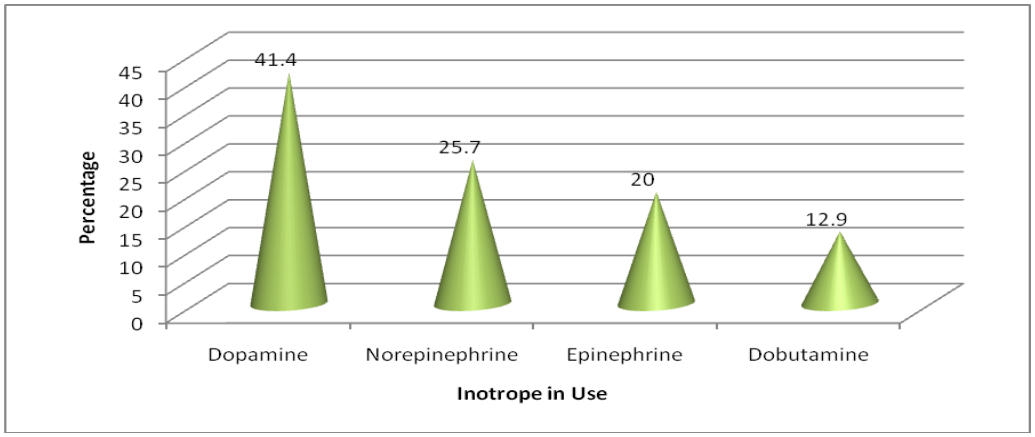
This was a survey on the use of vasopressor and inotropic agents over three months at the Kenyatta National Hospital. A total of 70 patients were recruited into the study. Of these 29 were male and 41 were female. Majority of the patients were between 25 and 35 years.The mean age was 34.6yrs.

Figure 2: A graph showing the age distribution of patients included in the study



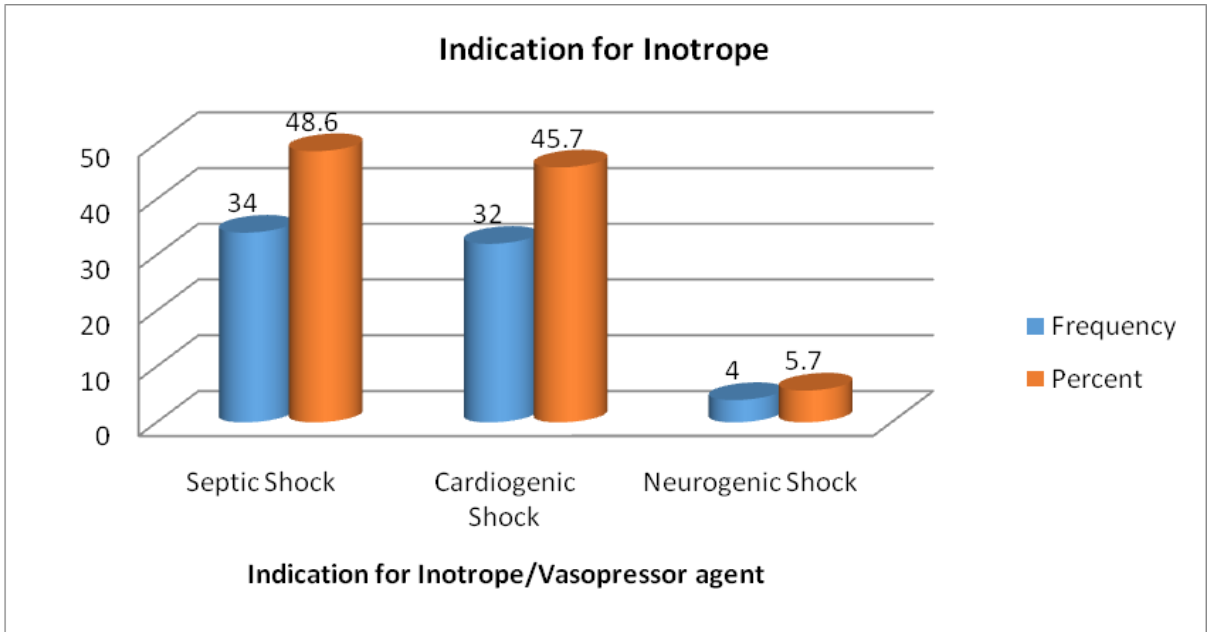
Through the study period four inotropes were available. Dopamine was most prescribed followed by norepinephrine.

Figure 3: The inotropes in use



Indications of inotropes were grouped into the different types of shock; septic, cardiogenic and neurogenic shock.

Figure 4: The indication for initiating inotropes



In the septic shock group the inotropes of choice were dopamine andnorepinephrine . There were 35 patients with septic shock. Of these 18 were on single inotrope while 17 were on double inotrope in the course of management as noted on table 3 below.

Figure 5: Choice of inotrope in the septic shock group

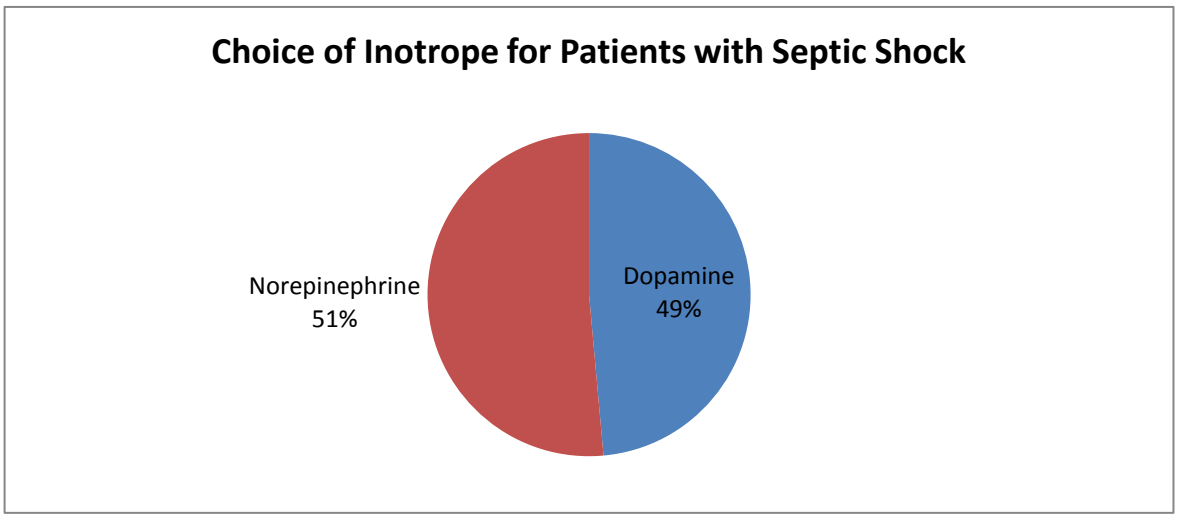


Table 3: Number of inotropes/vasopressor used in septic shock

Septic Shock	Frequency	Percentage
Single Inotrope	18	51.4
Double Inotropes	17	48.6

There were 32 patients with cardiogenic shock. 23 were post open heart surgery. The inotropes on choice were dobutamine, dopamine and epinephrine as presented on table 4 below.

Table 4: inotrope choice in cardiogenic shock

Inotrope	Frequency	Percentage
dobutamine	**9**	**28.1**
dopamine	**9**	**28.1**
epinephrine	**14**	**43.8**

The patients post open heart surgerywere either on single or double inotropes in the course of management as presented on table 5 below.

Table 5: Number of inotropes post open heart surgery

Heart Surgery	Frequency	Percentage
Single Inotrope	**20**	**87.0**
Double Inotrope	**3**	**13.0**

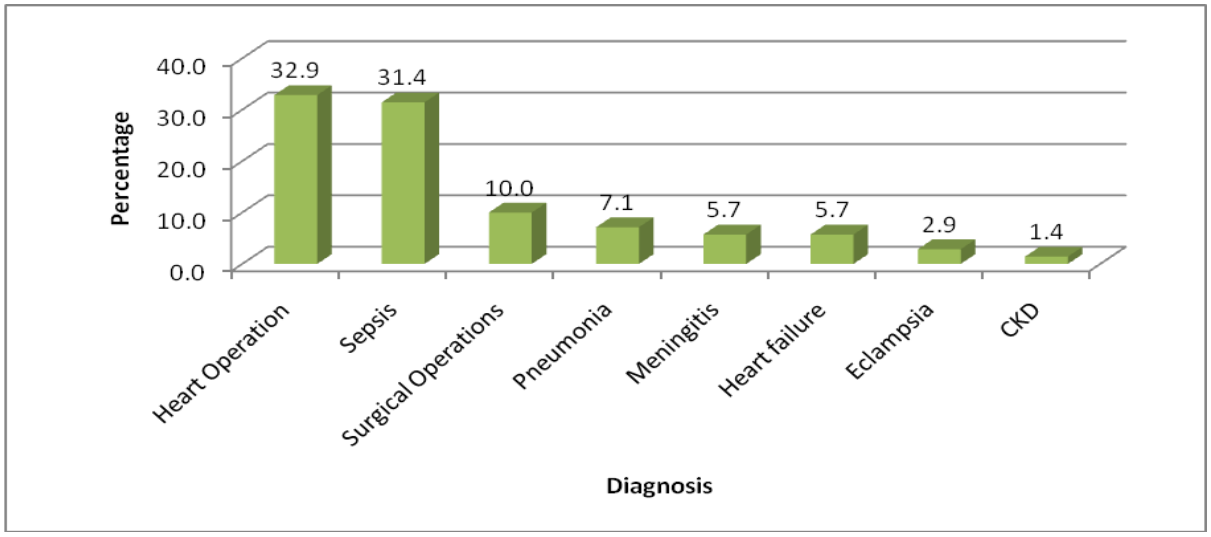
Inotrope choice in paediatric patients in the study presented on table 6 below.

Table 6: inotropes used on paediatric patients

Inotrope	Frequency	Percentage
Dopamine	2	50
Norepinephrine	2	50

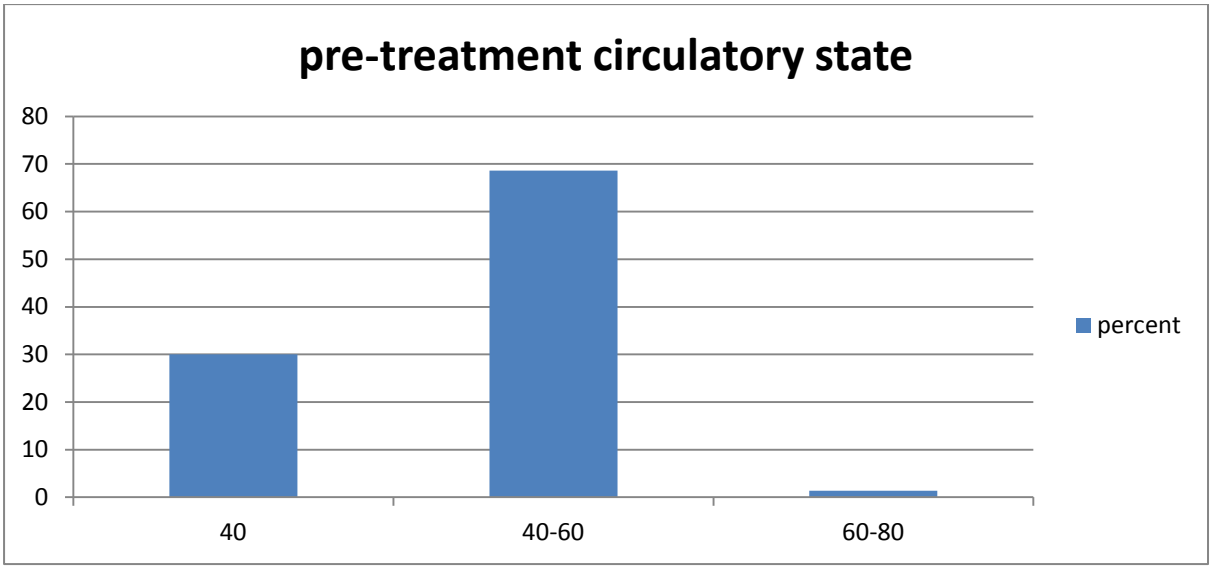
Patients had various admitting diagnosis in the different critical care areas. Majority of the patients were post open heart surgery and sepsis

Figure 6: Admitting diagnosis



Pre-treatment circulatory state of the patients was based on mean arterial pressure. Majority of the patients had a mean arterial pressure 0f between 40-60mmHg .

Figure 7: Pre-treatment circulatory state



In the group of patients with MAP of < 40mmHg majority had septic shock as shown on table 7 below.

Table 7: Type of shock in those with pre-treatment MAP <40mmHg

Pressure <40	Frequency	Percentage
Septic shock	19	90.5
Cardiogenic	2	9.5

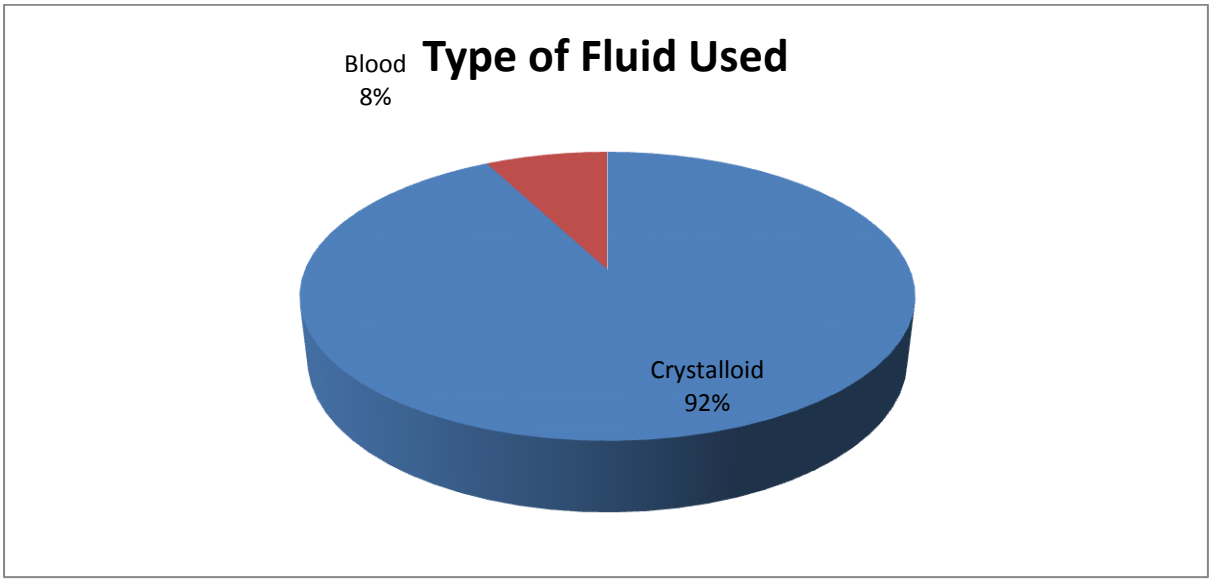
Fluid resuscitation in response to the hypotension was done on 39 patients while 31 of the patients were not fluid resuscitated. Majority of the patients who were fluid resuscitated had septic shock as shown on table 8 below.

Table 8: Type of shock among patients that were fluid resuscitated

Type of shock	**Frequency**	**Percentage**
Cardiogenic Shock	**2**	**5.1**
Neurogenic Shock	**3**	**7.7**
Septic Shock	**34**	**87.2**

Patients were either resuscitated with crystalloids or blood as shown by the pie chart below.

Figure 8: Type of fluid used for resuscitation



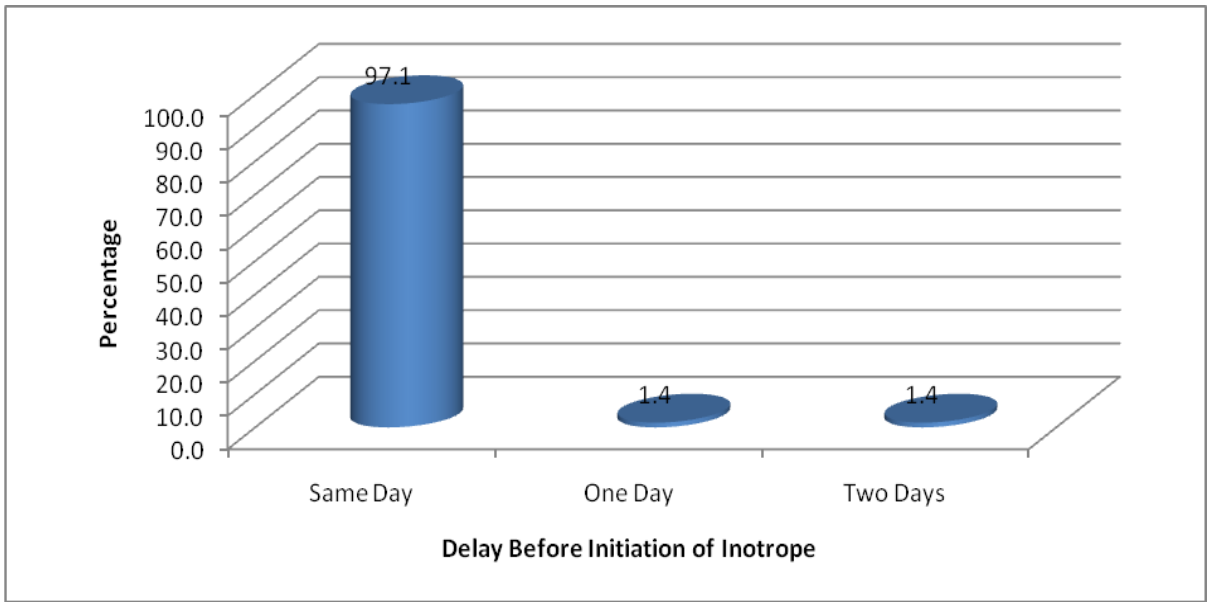
In the group of patients who were not fluid resuscitated most of the patients had cardiogenic shock.

Table 9: Patients who were not fluid resuscitated

Type of shock	Frequency	Percentage
Cardiogenic Shock	**30**	**93.8**
Septic Shock	**2**	**6.2**

Initiation of inotropes/vasopressor was either on the same day, one day later or two days later from time of prescription. 97% of the time, the agents were initiated on the same day they were prescribed as shown on figure 9 below.

Figure 9: Time of inotrope initiation from time of prescription



Through the study period patients were either on single or double inotropes. None of the 70 patients recruited were on three inotropes at any time. Dopamine was top as first inotrope while norepinephrine was top as being initiated as the second inotrope. This is depicted on figure 10 and 11 below.

Figure 10: first inotrope of choice

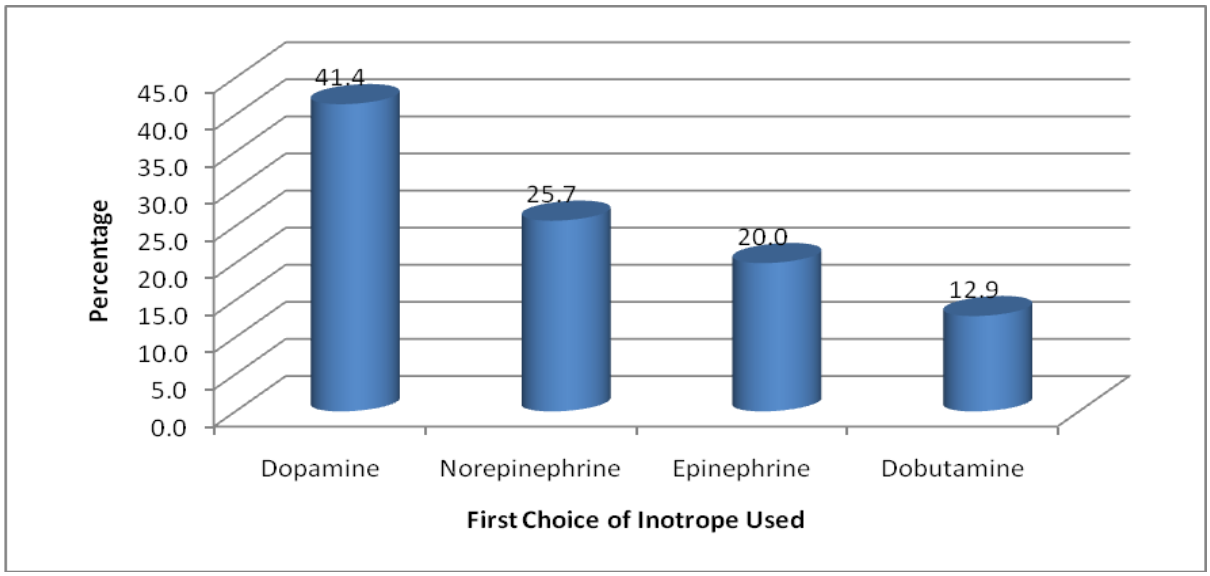
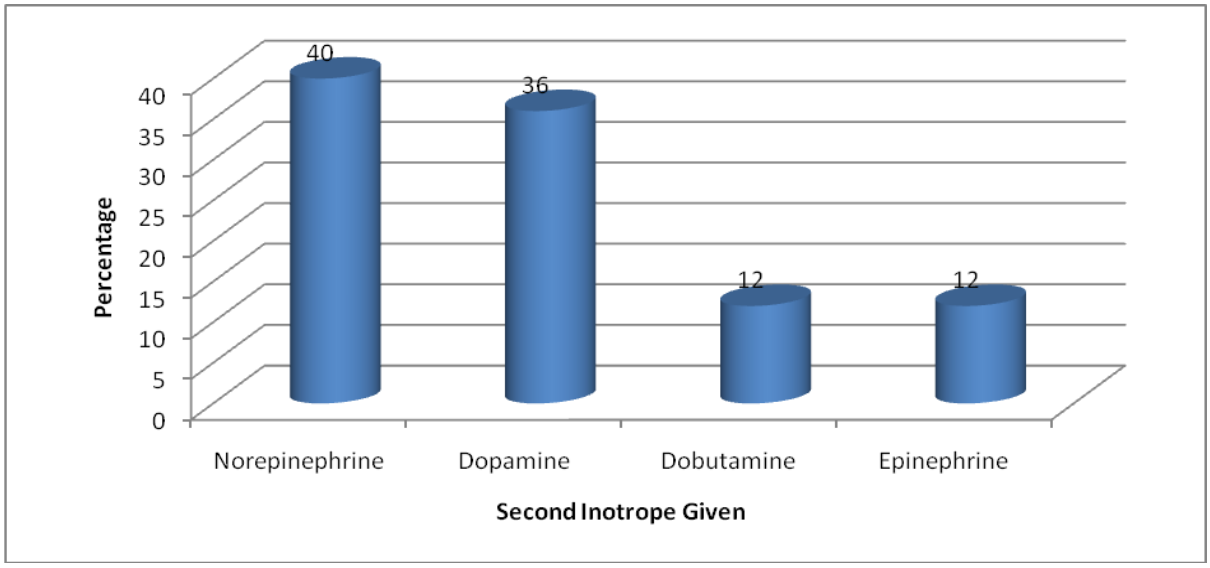
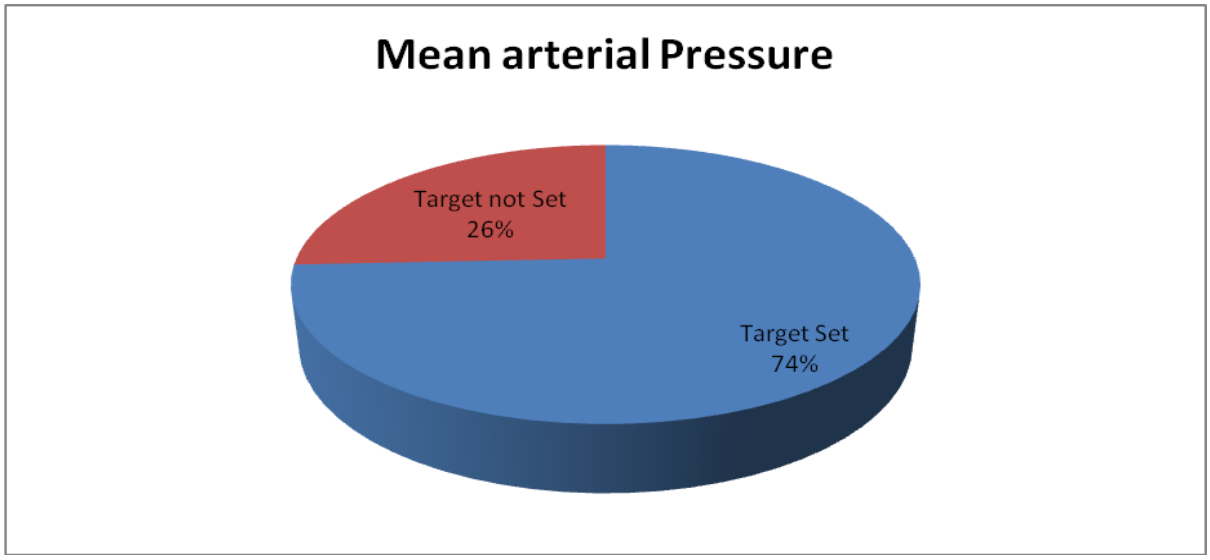


Figure 11: second inotrope of choice



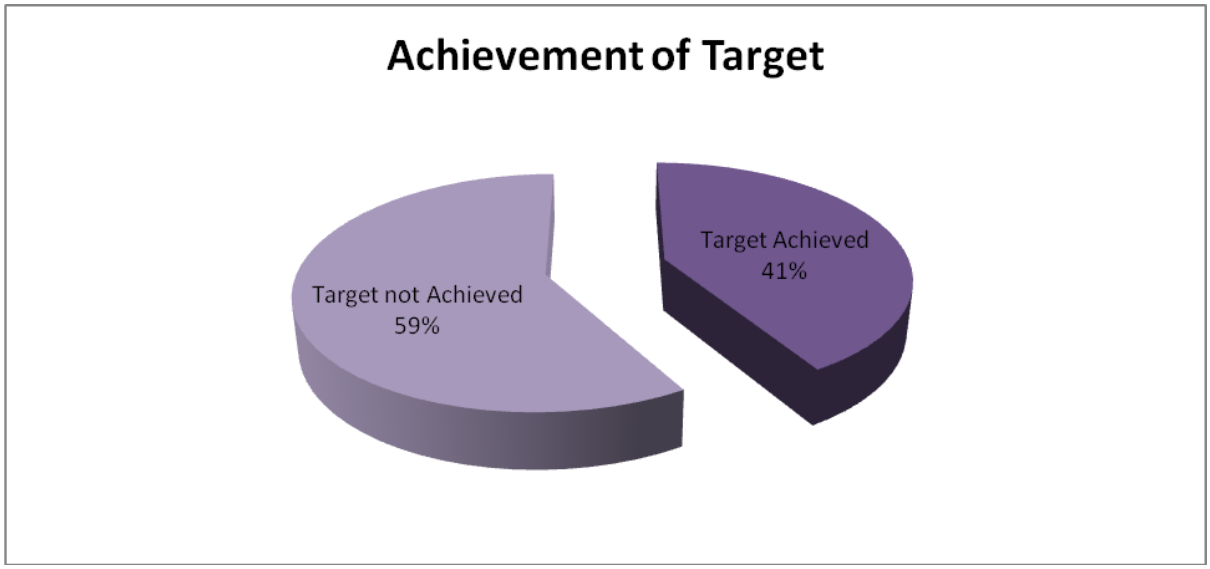
When inotropes are prescribed the clinician is meant to set and document a target mean arterial pressure. Figure 12 below shows the distribution.

Figure 12: Mean arterial pressure set target



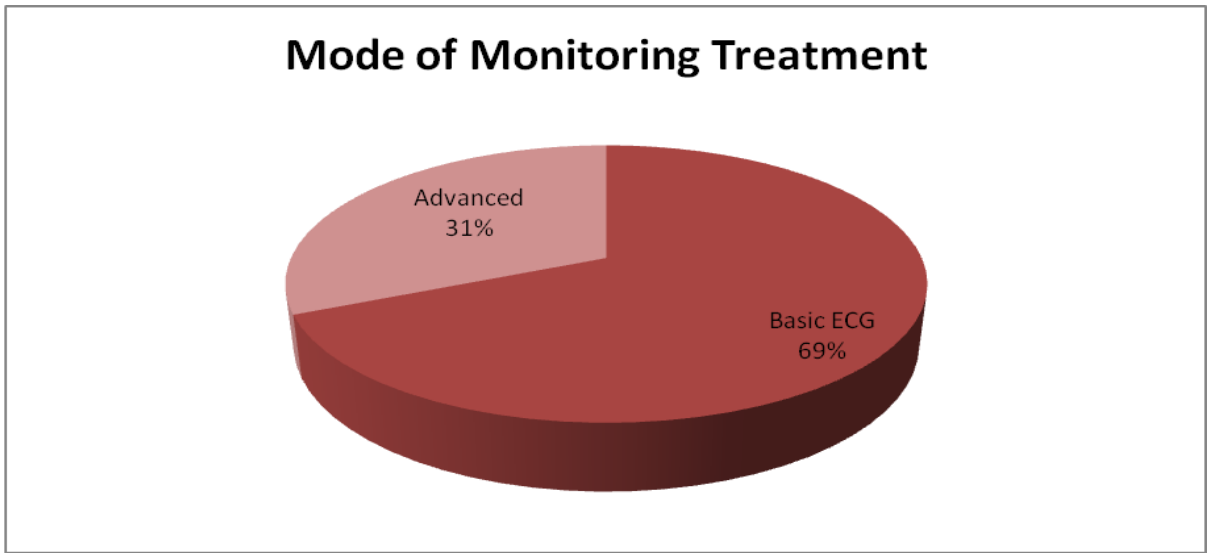
For inotropes/vasopressors to be weaned off the patient must achieved the set target mean arterial pressure.

Figure 13: achievement of target



Mode of monitoring patients was grouped into either basic or advanced. In this study basic monitoring included ECG, non-invasive BP, heart rate and central venous pressure. Advanced monitoring included invasive BP and central venous oxygen concentration. Basic monitoring was most used.

Figure 14: Mode of monitoring treatment



To administer the inotropes infusion pumps were used 100% of the time.

DISCUSSION

Inotropes and vasopressors are lifesaving agents used on the critically ill patients who present with hypotension that is unresponsive to fluid resuscitation. At Kenyatta National Hospital the critically ill patients are taken care off in the main critical care unit, emergency ward in casualty and high dependency units. There were a total of 70 patients recruited in the study. Majority were female patients. Age distribution was from as young as month old to as old as 75yr, this is because there is currently no separate paediatric critical care unit.

Through the study period the inotropes/vasopressors used were: norepinephrine, dopamine, dobutamine and epinephrine. These are the agents that are currently present in the pharmacy drug formulary. There is a wider range of inotropes that could be used though not available at the hospital.Drugs such as vasopressin and phenylephrine would be useful additions. Vasopressin is useful in septic shock that is resistant to dopamine, norepinephrine and epinephrine (7). Phenylephrine is the drug of choice in neurogenic shock. Dopamine was the most used inotrope (41.4%) followed by norepinephrine (23.7%). This is comparable to a study on inotropes and vasopressors in Scandinavian intensive care units where dopamine was used most (47%) followed by norepinephrine (40%).(6)

The indication to start inotropes/vasopressors was in terms of type of shock diagnosed. Septic shock was the leading indicator to initiate inotrope therapy followed by cardiogenic shock and lastly neurogenic shock. This is possibly due to the fact that at KNH the CCU admits all types of patients as compared to other centres that have specialized ICUs. Though grouped into the different types of shock the patients had varied admitting diagnoses as shown on figure 6. In comparable studies main indications to initiate inotropes is hypotension and oliguria (16). In this study hypotension was 100% the reason for initiating inotropes/vasopressors.

Dopamine and norepinephrine were the inotropes of choice in patients with septic shock. This is in keeping with international guidelines (4). Norepinephrine was prescribed as the first inotrope in 51% of the patients with septic shock. In a comparative study between norepinephrine and dopamine, norepinephrine was found to be strongly related to favourable outcome though there was no significant difference in mortality rate (5, 6). Among the patients with septic shock double inotrope was at 48.6%. Therefore, there is 50% chance of being on double inotropes when managing septic shock. In septic shock not responsive to dopamine and norepinephrine epinephrine is the alternative. In this study epinephrine was not used on patients with septic shock though it's available. Vasopressin is to be used when septic shock is resistant to all the three inotropes though it is not available in KNH.

Cardiogenic shock was mainly experienced by patients post open heart surgery. Inotropes of choice among these patients were dobutamine, dopamine and epinephrine as shown on table 4. These results are comparable to a study in Germany among patients with low cardiac output syndrome (LCOS) epinephrine (41.8%) was found to be the commonest. Followed by dobutamine (30.9%) and phosphodiesterase (14.8%) (10).

In terms of number of inotropes used in the management of cardiogenic shock, single inotrope use was at 87% and double inotrope was 13%. In a French multicentre survey of patients post cardiac surgery single inotrope use was 64%, double inotrope 26% and three inotropes 6%. During the study period no patient was on three inotropes (9). This may be possible because patients undergo triage before open heart surgery at KNH and therefore have a better cardiac status therefore less need for inotropes post-operatively while the type of cardiac surgery among patients recruited in French study was emergency and interventional.

In the paediatric age group dopamine and norepinephrine were the inotropes that were chosen. According to international guidelines dopamine is the first line of inotrope in children with shock and hypotension.

Pre-treatment circulatory shock offers a guide in the management of patients in shock. Ideally a MAP <60mmHg warrants the initiation of inotropes. In this study 68.9% of patients were started on inotropes when MAP was between 40-60mmHg. The patients with a pre-treatment circulatory MAP of <40mmHg had septic shock while patient started o inotropes when MAP was 60-80mmHg had neurogenic shock. In the neurogenic patients inotropes are initiated at a higher MAP in order to maintain cerebral perfusion pressure. In the paediatric group the clinical features of shock were used to start inotropes as compared to adults where MAP was the guide to initiate inotropes.

Prior to initiation of inotropes/vasopressor therapy fluid resuscitation is recommended. 55.7% of patients were resuscitated. Most of who had septic shock. Crystalloids were used mostly in resuscitation.

In assessing delay in initiation of inotropes it was found that 97% of the patients received treatment on the same day it was prescribed. Though initiated on the same day it wasn't possible to ascertain the exact point the inotrope was initiated. This is important as there is a difference in initiating treatment immediately versus hours later though within the same day. Only 2 patients had delay in treatment initiation that may have been attributed to poor documentation of instructions.

On prescribing inotropes/vasopressors the clinician is meant to clearly document the target MAP. Target was documented in only 74% of the cases.

Achieving the set target MAP meant that the patient was weaned off inotropic support. This was achieved in 41% of the patients. Patients in whom target wasn't achieved succumbed in the course of the study. The cause of mortality wasn't in the scope of this study as other factors may have contributed to mortality and the duration of the study was limited.

Mode of monitoring treatment was either basic or advanced. As per this study basic monitoring included non-invasive BP, heart rate, central venous pressure. Advanced monitoring included invasive BP and central venous oxygen saturation. Basic monitoring is the minimally acceptable modes of monitoring to ensure safety and adequacy of monitoring. 69% of patients were on basic monitoring while 31% were on advanced monitoring. This is acceptable as all the patients were adequately monitored.

Infusion pumps were used to administer inotropes/vasopressors to all the patients. This is the acceptable international standard of administering inotropes. During the study it was observed that quick change was the method of choice in substituting infusion of inotropes. It is associated with a drop in BP while changing the syringes though it is cost-effective compared to double pumping (20).

CONCLUSIONS

1. Dopamine is the most used inotrope at Kenyatta National Hospital.
2. 97% of the time inotropes were initiated on time; on the same day they are prescribed
3. Commonest indication for inotropes is septic shock.
4. There is adequate monitoring of patients on inotropic therapy.
5. There is proper administration of inotropes by use of infusion pumps

RECOMMENDATIONS

1. Creation of an inotrope chart that will aid in proper documentation as the treatment is ongoing.

2. A larger study over a longer period to assess other factors such as complications and outcome of patients on inotropes.

3. Development of guidelines on inotrope use to aid in management of patients.

4. Expand pharmacy formulary to include other inotropes/vasopressors.

Appendix 1

Consent for participation

Consent explanation.

My name is Dr. Simiyu Victoria M., a postgraduate student in Anaesthesia at the University of Nairobi. As part of my course work I am required to perform clinical research. I am conducting a study at the Kenyatta National Hospital on the use of inotropes and vasopressor in KNH CCU, HDU and Emergency ward. These drugs are used to correct low blood pressure and also enhance the pumping of the heart. The aim of this study is to help doctors improve the care given to patients. To do this, I will review the notes on your relatives file and observeon-going treatment. Thereafter I will do statistical calculations on this information and publish it in a book that will be in the custody of the University of Nairobi. All information gathered will be treated with utmost confidentiality. No names or other identifiers will be used in the study. As a consequence I shall need your consent for your relative to be included in the study. There are no risks involved in participating in this study. The benefits are that management will be optimized should a shortcoming be encountered.
Their participation in this study is voluntary and you may withdraw your relative at any point without affecting the treatment being given to them in any way. Any information obtained in the course of the study is beneficial in the management of the patient.

For further information and clarification you may contact:

Dr. Simiyu Victoria M. Telephone number – 0721396190
Dr. Murithi/Dr. Nabulindo – supervisors. Telephone number – 0722850375/0721418587
KNH/UON – Ethics & Research Committee. Prof. A.N. Guantai, Chair, Telephone number – 2726300 Ext. 44102

Statement by the researcher:

I confirm that the participant/next of kin was given an opportunity to ask questions about the study, and all the questions asked by the participants have been answered. I confirm the individual has not been coerced to participate in the study and the consent has been given freely and voluntarily.

Name:_____

Signature:_____

Date:_____

Consent Form

I _____ have been explained the purpose and conditions of my relative's involvement in the study by Dr.Simiyu Victoria M. I agree to the above and do give consent for _____ to be included in the study who is my relative, by virtue of being a……..

Name: _____ Witness Name: _____

Signature: _____ Signature: _____

Thumb print: _____ Thumb print: _____

Date: _____ Date: _____

Consent Form for patients who consent themselves

I _____ have been explained the purpose and conditions of my involvement in the study by Dr. Simiyu Victoria M. I agree to the above and do give consent to be included in the study.

Name: _____ Witness Name: _____

Signature: _____ Signature: _____

Thumb print: _____ Thumb print: _____

Date: _____ Date: _____

Idhini ya kushiriki katika utafiti

Maelezo.

Jina langu ni Daktari Simiyu Victoria M., mwanafunzi wa shahada ya pili katika chuo kikuu cha Nairobi. Kama sehemu ya masomo yangu ninastahili kufanya utafiti wa kitabibu. Lengo langu ni kufanya utafiti katika Hospitali ya Taifa ya Kenyatta juu ya matumizimadawa ya inotropes na vasopressors (haya ni madawa yanayowezesha moyo kupiga na pia husaidia kupandisha presha ya damu ili viungo vyote vya mwili vipate damu) katika wadi ya watu wenye hali mahututi. Lengo la utafiti huu ni kusaidia madaktari kuboresha huduma unaotolewa kwa wagonjwa. Kwa kufanya hivyo, nitakuuliza maswali na kutazama matibabu. Baada ya hapo nitafanya mahesabu ya takwimu na taarifa hii na kutangaza habari hiyo katika kitabu ambayo itakuwa chini ya ulinzi wa Chuo Kikuu cha Nairobi. Taarifa zote zilizokusanywa zitashughulikiwa na usiri. Hakuna majina au vitambulisho vingine zitakavyotumika katika utafiti. Kwa hiyo nitahitaji idhini yako kwa mwenzako (au tegemezi) kuwa mshiriki katika utafiti huu.

Ushiriki wako katika utafiti huu ni kwa hiari yako na unaweza kuondoa mwenzako (au tegemezi) katika hatua yoyote bila kuathiri matibabu atakayopewa mwenzako (au tegemezi) kwa njia yeyote. Taarifa zote zitakazopatikana katika mwendo wa utafiti huu ni manufaa kwa mgonjwa.

Kwa maelezo zaidi na ufafanuzi, unaweza kuwasiliana na:

Daktari Simiyu Victoria M. Nambari ya simu – 0721396190

Dr. Murithi/Dr. Nabulindo Nambari ya simu – 0722850375/0721418587

KNH/UON – Ethics & Research Committee. Pof. A.N. Guantai,Mwenyekiti, Nambari ya simu – 2726300 Ext. 44102

Idhini

Mimi _____ nimeelezewa madhumuni na masharti ya ushiriki wa mwenzangu (au tegemezi) katika utafiti na Daktari Simiyu Victoria M. Nakubaliana na maelezo hayo na nimemruhusu daktari kufanya utafiti huo kwa mwenzangu _____.

Jina: _____ Jina la mshahidi: _____

Sahihi: _____ Sahihi: _____

Finyo kidole cha gumba: _____ Finyo kidole cha gumba: _____

Tarehe: _____ Tarehe: _____

Idhini

Mimi _____ nimeelezewa madhumuni na masharti ya ushiriki wangu katika utafiti na Daktari Simiyu Victoria M. Nakubaliana na maelezo hayo na nimemruhusu daktari kufanya utafiti huo kwangu .

Jina: _____ Jina la mshahidi: _____

Sahihi: _____ Sahihi: _____

Finyo kidole cha gumba: _____ Finyo kidole cha gumba: _____

Tarehe: _____ Tarehe: _____

Appendix 2

QUESTIONAIRE **Number.....**

BIODATA

Age:..... Sex: M F

Diagnosis:.....

1. Indication for inotrope/vasopressor agent
    - Septic shock
    - Cardiogenic shock
    - Anaphylactic shock
    - Neurogenic shock
2. Underlying condition:……..
3. Pre-treatment circulatory state-MAP(mmHg)
    - 60-80
    - 40-60
    - ≤40
4. Was the patient fluid resuscitated

- yes
- no

5. if yes No.4, what was used and what amount?

- Crystalloid.....
- Colloid.....
- Blood.....

6. First choice of inotrope/vasopressor agent

DRUG	DOSE
• dobutamine	
• dopamine	
• epinephrine	
• isopreterenol	
• norepinephrine	
• phenylephrine	
• Vasopressin	

7. Day of inotrope/vasopressor initiation

Date of admission	Date of diagnosis requiring inotrope	Date of inotrope initiation

8. Did clinician set target mean arterial pressure:

- Yes
- No

9. Was a second inotrope/vasopressor needed:

    - Yes
    - No

10. Second inotrope/vasopressor initiated

DRUG	DOSE
o Dopamine	
o dobutamine	
o epinephrine	
o norepinephrine	
o phenylephrine	
o Vasopressin	

11. Was a third inotrope/vasopressor needed:

- Yes
- No

if yes,which one:.....

12. Was the target achieved:

- Yes
- No

13. Mode monitoring treatment

- Basic-ECG, NON-INVASIVE BP, HEART RATE, CENTRAL VENOUS PRESSURE
- Advanced-INVASIVE BP, CENTRAL VENOUS OXYGEN CONCENTRATION

14. What mode of administration was used?

- Infusion pump
- Other.....

Appendix 3: approval letter

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH/UON-ERC
Email: uonknh_erc@uonbi.ac.ke
Website: www.uonbi.ac.ke

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/172 Link:www.uonbi.ac.ke/activities/KNHUoN 5th June 2014

Dr. Simiyu Victoria M
Dept.of Anaesthesia
School of Medicine
University of Nairobi

Dear Dr. Simiyu

Research proposal: A survey on the use of Vasopressor and inotropic agents over three Months at the Kenyatta National Hospital (P32/01/2014)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 5th June 2014 to 4th June 2015.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN.**

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chairperson, KNH/UoN-ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UoN
The Chairman, Dept.of Anaesthesia, UoN
Supervisors: Dr. J.M. Muriithi, Dr.S. Nabulindo

REFERENCES

1. Prof. Gannon-inotropes. Available from http://profgannon,wikispaces.com/inotropes.

2. Guyton & Hall Textbook of Medical Physiology-12th Edition-John E. Hall PhD, Arthur C. GuytonProfessor& Chair Department of Physics & Biophysics.

3.Nalaka G., Scott M.- Physiology and principles of the use of vasopressors and inotropes.

4.DellingerRP,LevyMM,CarletJM,etal.SurvivingSepsisCampaign:InternationalGuidelinesfor Managementof SevereSepsisand SepticShock:2008.CritCareMed.2008

5. Comparison of dopamine and norepinephrine in the treatment of shock.

De Backer D, Biston P, Devriendt J, et al.

6. Martin C, Viviand X, Leone M, et al. Effect of norepinephrine on the outcome of septic shock. CritCare Med. 2000 Aug; 28(8):2758-65.

7.Role of vasopressin in the management of septic shock.
Mutlu GM, Factor P.Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine.

8.Antman EM, Anbe DT, Armstrong PW, et al. Acc/Aha Guidelines for the Management of Patients with St-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). 2004 Aug 31; 110(9):e82-292.

9.French multicentre survey on the use of inotropes after cardiac surgeryOlivier Bastien, Benoit Vallet,and the French Study Group AGIR (Agents Inotropes en chiRurgie cardiaque)

10.Current practice of hemodynamic monitoring and vasopressor and inotropic therapy in post-operative cardiac surgery patients in Germany: results from a postal survey.Kastrup M, Markewitz A, Spies C, et al.

11. Christopher B., Vlamidir D.-Inotropes and vasopressors. Review of physiology and clinical use in cardiovascular disease-ahajournals 2008:118;1047-1056

12. DuchesneJC,McSwainNE,Jr.,CottonBA,etal.Damagecontrolresuscitation:Thenewfaceof damagecontrol.J Trauma.Oct; 69(4):976-90.

13. SperryJL,MineiJP,FrankelHL,etal.Earlyuseofvasopressorsafterinjury:Cautionbefore constriction.J Trauma.2008Jan;64(1):9-14.

14. BeekleyAC.Damagecontrolresuscitation:Asensibleapproachtotheexsanguinating surgicalpatient.CritCareMed.2008Jul;36(7Suppl):S267-74.

15. Intesivmed R.J. Kusack, J.A.S Ball, A. Rhodes, et al Improving post operative morbidity and mortality 36.597-577/2002

16. Department of Anaesthesiology & Intensive Care, Karolinska Hospital, Stockholm, Sweden.

17. French multicentre survey on the use of inotropes after cardiac surgery, Olivier Bastien, Benoit Vallet and , the French Study Group AGIR (Agents Inotropes en chiRurgie cardiaque) Crit Care. 2005; 9(3): 241–242

18. Clinical practice parameters for haemodynamic support of paediatric& neonatal septic shock; 2007 update from American College of Critical Care Medicine

19. Quick change versus double pump while changing the infusion of inotropes: an experimental study.de Barbieri I, Frigo AC, Zampieron A.

20. Kothari C. R. Sample size determination. Research Methodology. New Age International Publications. 2004;174-175.