SAFETY OF PERIPHERAL INTRAVENOUS ADMINISTRATION OF VASOPRESSOR AGENTS IN RESOURCE-LIMITED SETTINGS

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DECLARATION

I hereby declare that this is my original work. This study has not been presented for a degree at any other university or college.

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LIST OF ABBREVIATIONS

CLABSI Central Line-Associated Bloodstream Infections

CLABSI Central Line-Associated Bacterial Systemic Infection

CVC Central Venous Catheter

KNH Kenyatta National Hospital

KNH/UoN-ERC Kenyatta National Hospital/University of Nairobi-Ethics Review Committee

PICU Paediatric Intensive Care Unit

PVC Peripheral Venous Catheter

SVR Systemic Venous Resistance

IQR Interquartile Ranges

OPERATIONAL DEFINITIONS

Vasopressors: Drugs used to constrict blood vessels or increase cardiac contractility e.g., adrenaline, noradrenaline, milrinone, dobutamine and dopamine.

Central venous catheter: A narrow, flexible tube inserted into one of the major veins (jugular, femoral etc.) to administer drugs or fluids.

Peripheral venous catheter: This is a thin flexible tube inserted into a vein. Used for drawing blood samples, and administering medications and fluids. Can be inserted on the scalp, back of the hand, lower arm or foot

Extravasation: The leakage of fluids from an intravenous line into tissues around it

ABSTRACT

Background: Vasopressors are conventionally administered through a central venous catheter (CVC) and not through a peripheral venous catheter (PVC) since the latter is believed to be associated with an increased risk of extravasation. Placement of a CVC requires suitably trained personnel to be on hand, and in resource-limited settings, this requirement may delay placement. Because of this and in cases where suitably trained personnel are not immediately available, some clinicians may be prompted to utilize a PVC for infusing vasopressors.

Objective: To determine the safety of peripheral intravenous administration of vasopressors among critically-ill children admitted at KNH

Methods: This was a prospective observational study conducted at Kenyatta National Hospital's paediatric ICU, main ICU and paediatric wards among admitted children aged between 1 month and 12 years. The participants were children on vasopressors through peripheral venous catheters. The study was estimated to take five months. The total sample was 49 children. Data collection was carried out using a standardized semi-structured questionnaire.

Data analysis: Continuous variables e.g., age in months were summarized using median and interquartile ranges (IQR).

Categorical variables e.g., gender (male/female), type of vasopressor and presence of extravasation or thrombophlebitis (yes/no) were summarized using frequencies and percentage proportions.

Factors associated with complications of peripheral intravenous administration of vasopressors e.g., the dose of vasopressor and duration of administration on complications (yes/no) were assessed using binary logistic regression. Results were evaluated at 5% significance level using p-values and odds ratios/confidence intervals for odds ratios. P-values less than 0.05 were considered significant.

Results: Of the 49 children, 31 (63.3%) were males. The median age was 21 months with an interquartile range of 10 to 28 months. The patients were admitted with septic shock except one with cerebral venous sinus thrombosis. The prevalence of extravasation injuries was 67% (95% CI 52%, 80%) and that of thrombophlebitis was 4% (95% CI 1%, 15%). The combined prevalence of vasopressor administration via peripheral lines was 69.4% (95% CI 54.4%,

81.3%). The extravasation injuries were grades one and two. The duration of cannula use of significantly associated with complications (P value <0.005), OR 1.14 (95% CI 1.05, 1.27). Age less than 2 years, upper limb cannulas and longer duration of inotrope infusion had higher odds of developing complications.

Conclusion: The extravasation injuries that occurred in this study were either grade one or two with the majority being grade one.

The prevalence of extravasation injuries in this study was high and incomparable to most of the findings from the literature.

The prevalence of thrombophlebitis was low and generally within the findings of the published literature.

Only one factor i.e., duration of cannula use was significantly associated with the development of complications of vasopressor administration via peripheral lines in children. Children less than two years, infusion of vasopressors on the upper limbs, smaller cannula gauge had higher odds of developing complications of vasopressor infusions via peripheral lines.

Recommendations: We recommend that larger multisite studies be conducted to ascertain the findings of high prevalence of extravasation injuries and assess the risk factors for the development of complications of vasopressor infusion via peripheral lines.

Utility of the study

The outcome of this study will help understand the safety of administering vasopressors through peripheral lines. If the study confirms that this practice is not safe, then we will recommend the use of central lines for the administration of vasopressors. If the practice is safe, then it will be recommended that vasopressors be administered peripherally since their safety is confirmed and it will help save time.

CHAPTER 1: INTRODUCTION

1.1 Background

Vasopressors or inotropes are drugs used mainly to cause vasoconstriction or improve cardiac contractility. These drugs are mostly used in the treatment of hypotension in children with septic shock. In septic shock, there is decreased blood supply to key organs. Vasopressors cause vasoconstriction leading to an increase in systemic vascular resistance (SVR). SVR increases mean arterial pressure. An increase in mean arterial pressure increases blood supply to organs (1).

Inotropes can be administered either through a peripheral venous catheter (PVC) or a central venous catheter (CVC). (2)(3) In resource-limited settings where central lines may not be available, these drugs can be administered through peripheral lines and this method is safe. (4) Timely administration of inotropes is necessary where the drug is urgently needed to save lives (3). Administration of vasopressors through a PVC reduces delays. (5) According to Abrar et al., 2022, early administration of inotropes has been shown to reduce mortality. (3)

Experts recommend the use of CVC in the administration of vasopressors to prevent infiltration. In resource-limited settings, a lack of experts in the insertion of CVCs delays the administration of inotropes (6). According to Turner & Kleinman, 2010 peripheral lines are safe to use in the administration of vasopressors as their data showed that administering inotropes through a PVC was safe, especially when given in short durations and small doses.

The adult sepsis surviving guidelines of 2020 have recommended the use of PVCs in starting vasopressors in situations where CVC is not feasible. (7) The pediatrics sepsis surviving guidelines of 2020 have not recommended neither have they prohibited its use. It is left open for the clinician to decide and this has been the practice. (8)

Due to the aforementioned challenges of fixing central lines in resource-limited settings, there is a need to generate data on the use of peripheral lines to infuse vasopressors. Most of the available data on this topic is from high-resource settings. Turner & Kleinman, 2010 concluded that their study showed that a small dose and short duration of administering inotropes through peripheral lines were safe. What then happens in settings where the drug has to be administered in large doses over long durations and CVCs cannot be inserted? Our study seeks to also

establish the difference in safety between small and high-dose inotropes and also correlate safety and duration of administration.

Studies show that the use of CVCs is advised by experts in administering inotropes (6). The use of peripheral lines is recommended for emergencies only especially in high-resource settings (9).

Risks of CVCs: CVCs do come with a set of complications e.g., insertion into the arteries which may lead to obstruction resulting in blood clots, vascular injury, hematoma and central line-associated bloodstream infections (CLABSI) (10).

The above complications may encourage the use of peripheral lines but their safety has to be confirmed in our setting. If the peripheral lines are safe, we are likely to reduce delays in administering inotropes which are life-saving, reduce the need for fixing central venous catheters (CVCs) which are also costly to patients, avoid complications of central lines e.g., CLABSI, pneumothorax, vascular injuries and hematoma. (10) Uncontrolled haemorrhage can occur when CVCs wrongly inserted into arteries are removed without taking caution (11)

Benefits of CVCs: A CVC decreases the frequency of injections, especially when drawing blood samples. Decreases the soreness that is usually linked with infusion therapy, and reduces anxiety among people who receive frequent intravenous fluids or need blood specimens drawn (12).

Risks of PVCs: Although PVCs are the most commonly used, PVCs when not well handled can lead to PVC-related bloodstream infections. In addition, PVCs are associated with thrombophlebitis and extravasation. (13)

Benefits of PVCs: the of PVCs has increased and is being used even in intensive care units and in cancer patients. The reason for this is due to their easy insertion, safety issues and are less costly. (14)

1.2 Problem statement

Studies in the literature agree that peripheral administration of inotropes is generally safe (3). Kumar et al. conclude that in resource-limited settings and under keen administration, peripheral administration of vasoactive drugs is safe. (9) According to Turner and Kleinman, results from their series of studies show that vasopressors can be administered through a PVC and it is safe. (6) However, some suggest that the safety depends on the amount of infused drug and the

duration of infusion [(3)(6)]. While complications of peripheral administration of vasoactive agents have been observed though, in small prevalence, these studies have not concluded that the practice is safe.(15)(16)(17) Because of this disparity, it is crucial to conduct more studies on this topic. The studies should compare the type of drug given, the amount infused/dose and the duration of infusion. This data will help determine the safety of peripheral lines in the administration of inotropes based on the above three aspects.

1.3 Significance of the study

As mentioned earlier, the administration of vasopressors is very crucial in a paediatric intensive care unit (PICU) among patients in shock. These drugs improve blood supply to organs and prevent multiorgan dysfunction. Reducing delays in administering these drugs is directly proportional to patient survival. The findings of this study will go a long way in informing whether peripheral lines are safe to use or not. If peripheral lines are found to be safe, delays in starting inotropes and complications of CVC insertion will be minimized.

CHAPTER 2: LITERATURE REVIEW

2.1 Background

Vasopressors are used to induce vasoconstriction and increase cardiac contractility (3). Vasoconstriction increases systemic vascular resistance which in turn increases mean arterial pressure which increases organ perfusion. Increased cardiac contractility increases cardiac output which in turn improves blood supply to the organs (18).

The recommended method of administration for vasopressors is infusion via a central venous catheter. However, administering these drugs via peripheral venous access reduces the need for central lines. Cardenas-Garcia et al., 2015 concluded that administering vasopressors via a peripheral line is safe and feasible (18).

Abrar et al., 2022 found a low incidence rate of extravasation as a result of peripheral intravenous administration of inotropes in a study conducted at Aga Khan University Hospital. In this study, adrenaline was the most used medication at 75.6%. Other inotropes used were milrinone, norepinephrine and dopamine.

2.2 Central venous catheters

Insertion of a central venous catheter is a common procedure. It is necessary, especially when caring for critically ill patients. It is a device that is inserted peripherally into a central vein i.e., internal jugular, femoral or subclavian veins. Used for the administration of fluids or medication. (19) The terminal lumen of central venous access resides in the inferior vena cava when inserted in the femoral vein, and the superior vena cava when inserted in the jugular vein or right atrium.

Benefits of central lines

A CVC decreases the frequency of injections, especially when drawing blood samples. Decreases the soreness that is usually linked with infusion therapy, and reduces anxiety among people who receive frequent intravenous fluids or need blood specimens drawn. (12)

Risks of central lines

With all the convenience that comes with central venous catheters, they also have their fair share of risks. Some of the known complications of central lines include; arterial injury if wrongly inserted which occurs in 1% of cases. In case the device is inserted into an artery, the formation

of thrombi is likely which can result in neurological deficit and stroke (11). In addition to the above, CVCs can also lead to lacerations of the vena cava, right atrium or formation of hematomas. Uncontrolled haemorrhage can occur when CVCs wrongly inserted into arteries are removed without taking caution (11). Central lines are also associated with CLABSI (10).

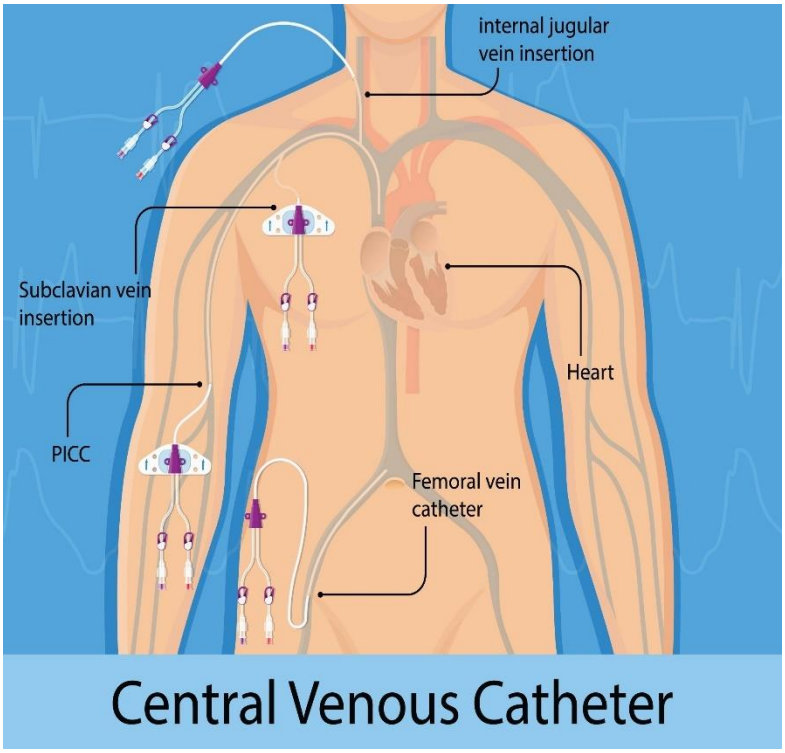


Figure 1:Pictorial representation of central venous catheter sites: From '***Preventing Complications of Central Venous Catheterization***' (20)

2.3 Peripheral venous catheters

This is a thin flexible tube inserted into a vein. Used for drawing blood samples, and administering medications and fluids. Can be inserted on the scalp, back of the hand, lower arm or foot (21). They are more commonly used compared to CVCs. Before insertion of CVCs, PVCs act as the first line route for administering life-saving medications e.g., vasopressors, fluid resuscitation and others.

Although they are the most commonly used, PVCs when not well handled can lead to PVC-related bloodstream infections (22). In addition, PVCs are associated with thrombophlebitis and extravasation.

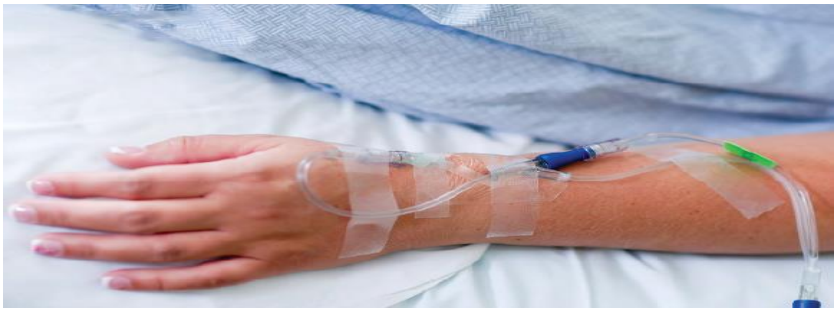


Figure 2: Pictorial representation of a peripheral venous catheter site

: From ***Peripheral Intravenous Access Using Ultrasound Guidance*** (23).

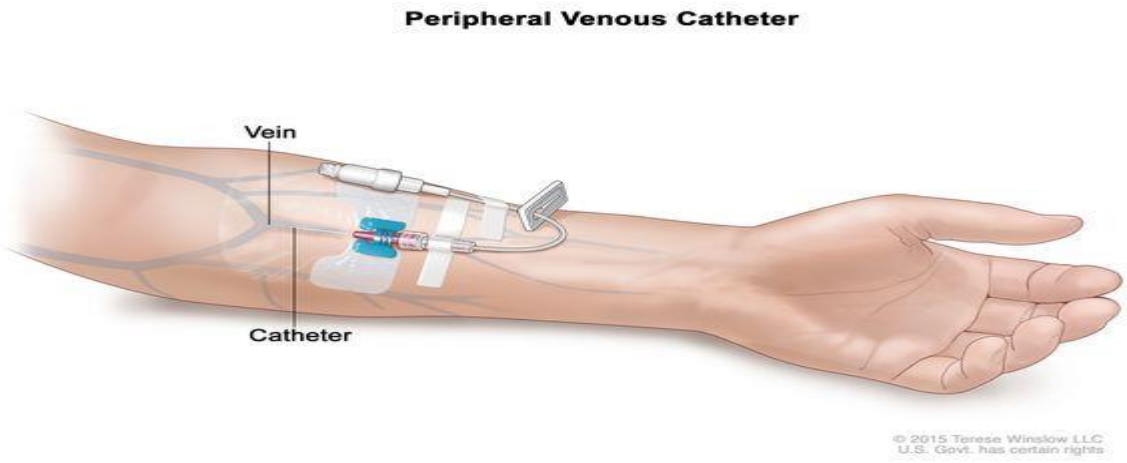


Figure 3: Pictorial representation of a peripheral venous catheter site

: From (21)

2.4 Complications associated with the administration of vasopressors through PVCs

As mentioned earlier, PVCs are commonly associated with bloodstream infections (22). However, other complications are mainly associated with the administration of vasopressors e.g., adrenaline, noradrenaline, dopamine, milrinone and other medications. The most common is extravasation and thrombophlebitis.

Extravasation

The leaking of plasma, lymph fluid, or other fluids, such as chemotherapy drugs, from a blood vessel or tube into the tissues surrounding it. Occurs with prolonged infusions. Also depends on the location of the PVCs, commonly in distal areas (4).

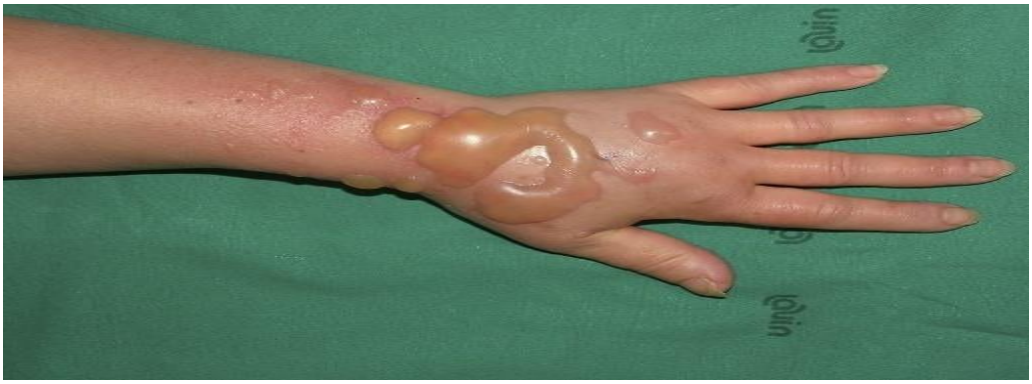


Figure 4: Early signs of extravasation; from (24)

Research shows that 11% of paediatric patients and up to 70% of neonates getting intravenous therapy do get extravasation injuries (25). About 50% of the intravenous lines fail, of these, 20% are thought to be due to extravasation and infiltration (13). Manifests by inflammation at the intravenous line, excessive pain, discolouration, numbness and altered blood flow.

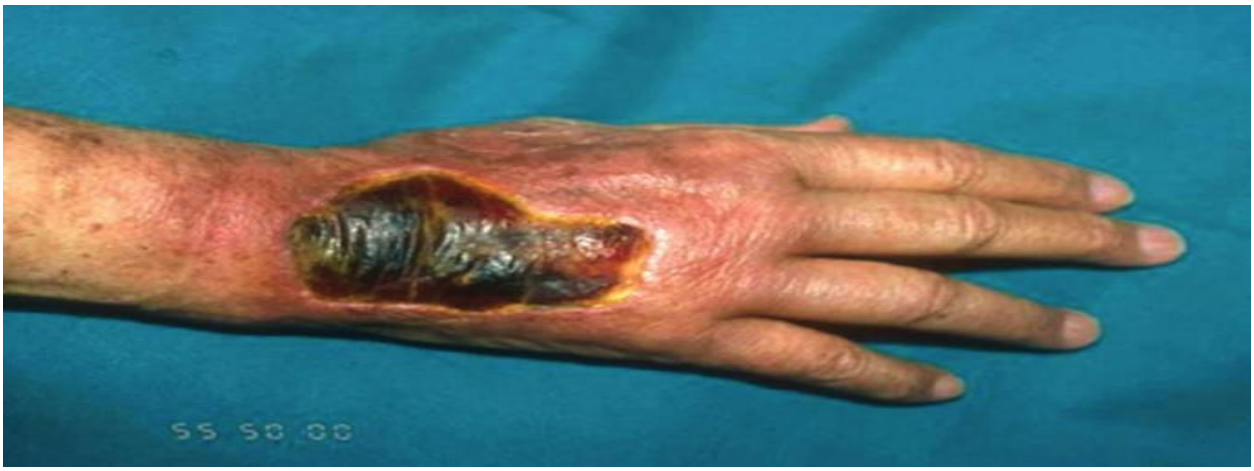
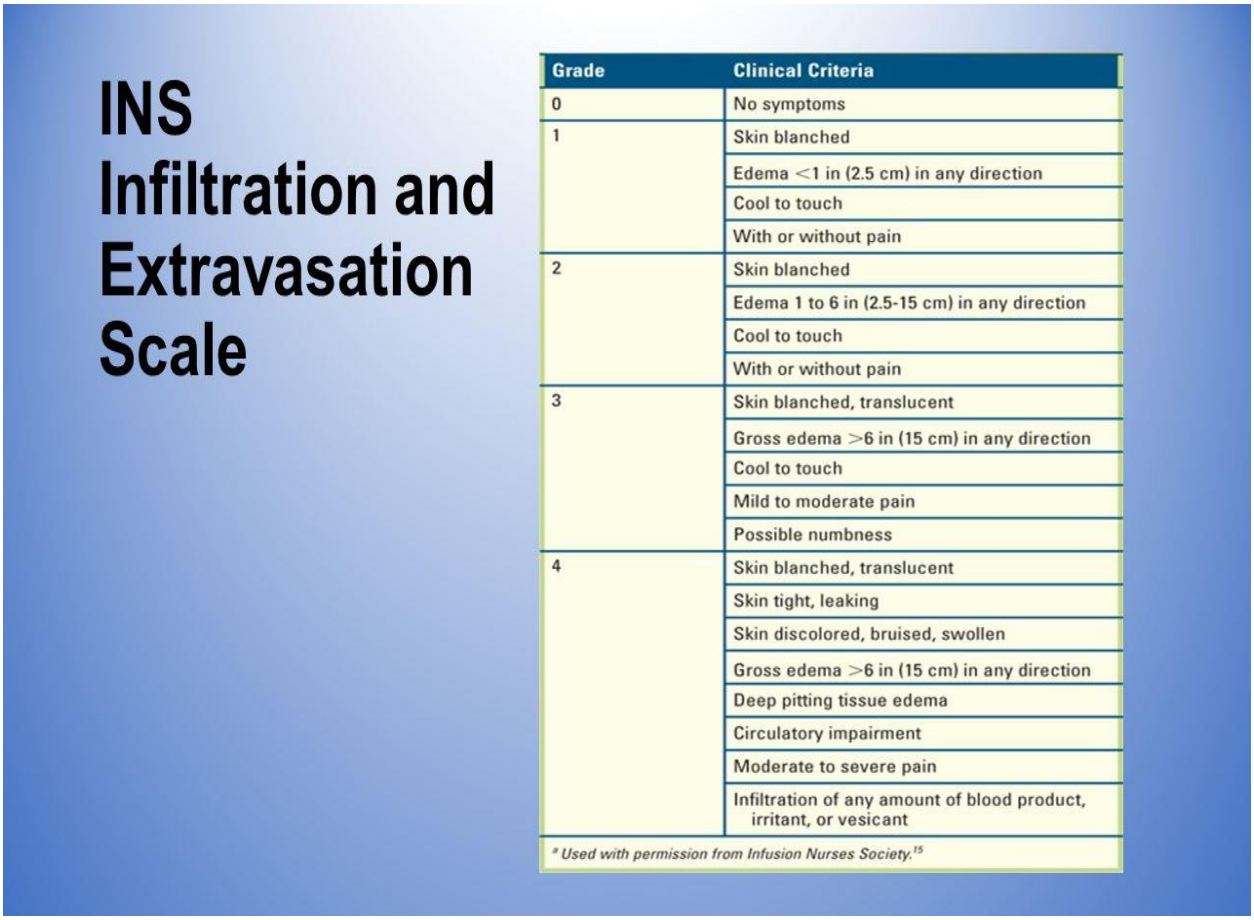


Figure 5: Extravasation

From '*Textbook of Plastic and Reconstructive Surgery* (26)

Classification of extravasation injuries

Table 1: Infiltration and extravasation scale; from (13)



INS Infiltration and Extravasation Scale

Grade	Clinical Criteria
0	No symptoms
1	Skin blanched
	Edema <1 in (2.5 cm) in any direction
	Cool to touch
	With or without pain
2	Skin blanched
	Edema 1 to 6 in (2.5-15 cm) in any direction
	Cool to touch
	With or without pain
3	Skin blanched, translucent
	Gross edema >6 in (15 cm) in any direction
	Cool to touch
	Mild to moderate pain
	Possible numbness
4	Skin blanched, translucent
	Skin tight, leaking
	Skin discolored, bruised, swollen
	Gross edema >6 in (15 cm) in any direction
	Deep pitting tissue edema
	Circulatory impairment
	Moderate to severe pain
	Infiltration of any amount of blood product, irritant, or vesicant

[a] Used with permission from Infusion Nurses Society.[15]

Management of extravasation includes discontinuing the infusion, detaching the giving set from the cannula and aspirating the content that is in the cannula. Antidotes can also be administered if known. The doctor should be notified if not around (27). Cold and warm wrappings are also recommended for fifteen to twenty minutes every four hours.

Thrombophlebitis

This is an inflammation that causes blood clots to occur. The clots can block one or more veins. There are two types of thrombophlebitis; superficial and deep vein thrombosis (28). In the context of drug administration, the most common risk factors include duration of infusion, type of drug and the solutions infused (29).

Peripheral vein thrombophlebitis occurs in 25% to 35% of hospitalized patients. It is associated with sepsis and economic implications (increases in the cost of treatment) on the patient (30). A study by (31) found increased incidences of peripheral thrombophlebitis. In addition, the incidence was high among patients whose cannulas were inserted into the back of the hand.

The treatment of thrombophlebitis is still poorly defined. The main aim is to prevent venous thromboembolism (32). Treatment can be done topically, surgically or medically. Surgical treatment entails the excision of the affected part of the vein which prevents recurrence (33). Medical treatment involves the use of drugs that reduces the formation of blood clots.

Administration of vasopressors through peripheral lines can also cause limb ischemia and tissue necrosis. (5)

2.5 Safety of peripheral intravenous administration of vasopressors

Many studies have been conducted on the peripheral intravenous administration of vasopressors. Most of these studies are from high-resource settings. Most of them have debated whether to use or not to use a peripheral venous catheter to administer vasopressors because of safety issues. The surviving sepsis campaign recommends initiating vasopressors using a peripheral line (34).

According to Abrar et al., 2022, their study found a 2.2% incidence rate of extravasation (3). They considered the method of administration as this rate was low and did not cause major damage. In Turner and Kleinman, 2010, a 15% rate of thrombophlebitis was observed within a median of 7 hours (6). The patients without extravasation in this study had a significantly lower duration of vasopressor administration. The risk for complications increased with higher doses and longer duration of administration. As much as peripheral intravenous administration of inotropes is generally considered safe, complications may depend on the duration of extravasation.

Kumar et al., 2015 found a 1.5% rate of extravasation in children undergoing peripheral administration of vasopressors. According to this author, central lines are ideal for the administration of vasopressors but in resource-limited settings, it is justifiable to use a peripheral line. This author attributes this conclusion to a lack of major adverse effects and cost-effectiveness (9).

Vasoactive agents administered via a PVC of gauge 18 and above through large veins e.g., external jugular or forearm veins are viable and harmless (4). In this study, only 1 out of 122 (0.8%) of the patients developed extravasation. This occurred after 52 hours of administration. The incidence of adverse events in the peripheral administration of vasopressors in children is low according to a meta-analysis by (35). These authors suggest that more research needs to be conducted taking into account the site of the PVC and size, the characteristics of the children and the type of vasopressors.

Noradrenaline used in higher doses than those commonly used may be necessary to reduce low blood pressure and increase perfusion in children (36). In addition, the administration of noradrenaline through peripheral or intraosseous lines is safe with no adverse effects.

In a retrospective study of 55 patients receiving norepinephrine via peripheral venous catheters, Overall, 6% of the patients developed complications. These complications were not major (37). The complications were extravasation 2(3.6%) and local thrombophlebitis 1 (1.8%). These authors suggest the conduction of larger future studies to determine patients to whom this mode of vasopressor administration is safe.

Inotropic drug administration through peripheral intravenous lines in children admitted to the paediatric ICU with shock was observed to have a low occurrence of infiltration and extravasation of fluids (38). There was also no subsequent tissue damage. Interim administration of vasopressors via peripheral intravenous access in a highly monitored PICU seems to be safe.

In Charbel et al., 2021, one patient 2.7% (95% CI 0.5-13.8 per cent) had extravasation. The intravenous access was a gauge-24 catheter in the hand. This patient developed skin hypoperfusion (17). With the minor complications of peripheral administration of vasoactive agents, the use of this method is safe, especially in resource-limited settings where risks are weighed against benefits. It will be beneficial to administer vasopressors via peripheral lines rather than risk multiorgan failure as a result of hypoperfusion.

A retrospective study conducted in the United Kingdom found a 3.5% adverse event rate among children who received vasoactive agents through a peripheral line compared to 2.5% in those who received the drugs through a central venous catheter (16). There was no significant difference in adverse events between the two groups. Another study by (15) found a 1.7%

adverse event rate among children who were administered vasopressors via peripheral venous access. These adverse events occurred mainly in the hands.

Table 2: Summary of the studies identified

Study title/ Author/year	Setting	Study design/study population/sample size	Vasopressor	Key findings
Safety of Vasopressor Medications through Peripheral Line in Pediatric Patients in PICU in a Resource-Limited Setting, Abrar et al, 2022		Prospective observational study, Children 1 month to 18 years Sample size = 369	Adrenaline Milrinone Noradrenaline	Extravasation observed in 2.2% of the patients
The Use of Vasoactive Agents Via Peripheral Intravenous Access During Transport of Critically III Infants and Children, Turner DA and Kleinman ME, 2010	Children's Hospital Boston	Retrospective observational study Neonates and paediatric patients Sample size = 73	Vasoactive drugs	Thrombophlebitis observed in 15% of the patients
Study of Vasoactive Infusions through Peripheral Line, Kumar et al, 2015	Institute of child health and Hospital for Children, Egmore, Chennai	Descriptive study Children aged 1 month to 12 years Sample size = 204	Adrenaline Noradrenaline Dopamine Dobutamine	Overall extravasation was 1.5%. Extravasation was 20% in those receiving adrenaline and 1.2% in those on dopamine
Complications from Administration of Vasopressors Through Peripheral Venous Catheters, Medlej et al.,2018		An observational study Sample size = 55	Norepinephrine	3.6% developed extravasation, 1.8% developed thrombophlebitis
Safety of early norepinephrine infusion through peripheral vascular access during transport of critically ill children, Charbel et al, 2021		Retrospective study Children less than 18 years Sample size = 37	Norepinephrine	2.7% of the patients developed extravasation
Peripheral and Central/Intraosseous Vasoactive Infusions During and After Pediatric Critical Care Transport, Peshiman et al, 2022	North Thames and East Anglia regions of the United Kingdom	Retrospective Cohort Study of Extravasation Injury Children aged 18 years and below Sample size = 558	Vasoactive drugs (adrenaline, dopamine, dobutamine	3.5% of patients developed extravasation with 1 resulting in tissue necrosis

			and noradrenaline)	
Peripheral Vasoactive Administration in Critically Ill Children with Shock, Levy et al., 2022	Quaternary PICU	Single-Center Retrospective Cohort Study Children aged one month to 18 years Sample size = 231	Vasoactive drugs	Extravasation occurred in 1.7% of the patients

2.6 Factors associated with the development of complications among children receiving vasopressors through the peripheral venous catheter

This section looks at the likely factors that expose children to vasopressors via peripheral lines to complications. The factors being considered here are the type of vasopressor, maximum average dose, duration of infusion and site of the cannula.

Abrar et al. in their study of the safety of vasopressors administered via peripheral lines in critically ill children did not find an association between maximum dose of epinephrine and norepinephrine with the development of extravasation. (3) The concentration of the vasopressor and infusion rate has been associated with the risk of developing extravasation when vasopressors are administered via a peripheral line. (39)

Longer duration of administration of vasopressors via peripheral lines among critically-ill children is associated with the development of complications e.g., thrombophlebitis and extravasation. (35)(39)(6) The location of the PVC has also been associated with the risk of complications of peripheral administration of vasopressors. Owen et al. report that PVCs inserted in the distal end of the extremities were more associated with the development of complications. (35) Despite various studies in the literature looking at the safety of vasopressor administration through peripheral lines, there are very few studies looking at the risk factors for the development of these complications.

Summary

The use of CVCs for intravenous administration of vasoactive agents is highly advised by experts. CVSs have also been shown to have complications e.g., arterial injuries, hematomas and CLABSI as indicated in the literature above. However, peripheral venous catheters (PVCs) are also widely used especially in resource-limited settings. The use of PVCs is generally safe.

Though they may have complications, they are minor and non-life threatening and their use is therefore acceptable. Longer duration of vasopressor administration, distal peripheral venous catheters, the concentration of vasopressors and the rate of infusion are associated with the development of complications.

2.7 Justification and Utility

As observed from the literature, experts highly recommend the use of central venous catheters in the administration of vasoactive agents (6). However, this may delay the administration of the life-saving agents, especially in resource-limited settings due to either unavailability of central lines or a lack of experts who can insert them. In addition, literature has also shown that the safety of peripheral intravenous administration of vasopressors is reduced by factors such as; the small size of the cannula, long duration of administration and higher doses of the agents (6). This contradicts (36) who concluded that larger than normal doses (the doses found in literature) of noradrenaline are safe. A systematic review by Tian et al. showed that extravasation was not common when vasopressors are given via PVCs for a limited time and under observation. (40)

Other studies have also recommended that more studies be done to explore the factors that may reduce or increase the safety of peripheral intravenous administration of vasopressors. Most of the available data is from high-resource settings. The current study will be conducted in a low-resource setting. In line with recommendations from the literature, other than looking at safety, we also aim to assess the factors that either increase or reduce the safety of peripheral administration of vasoactive agents e.g., the dose of the drug, type of drug, duration of administration and location of the cannula.

2.8 Conceptual Framework

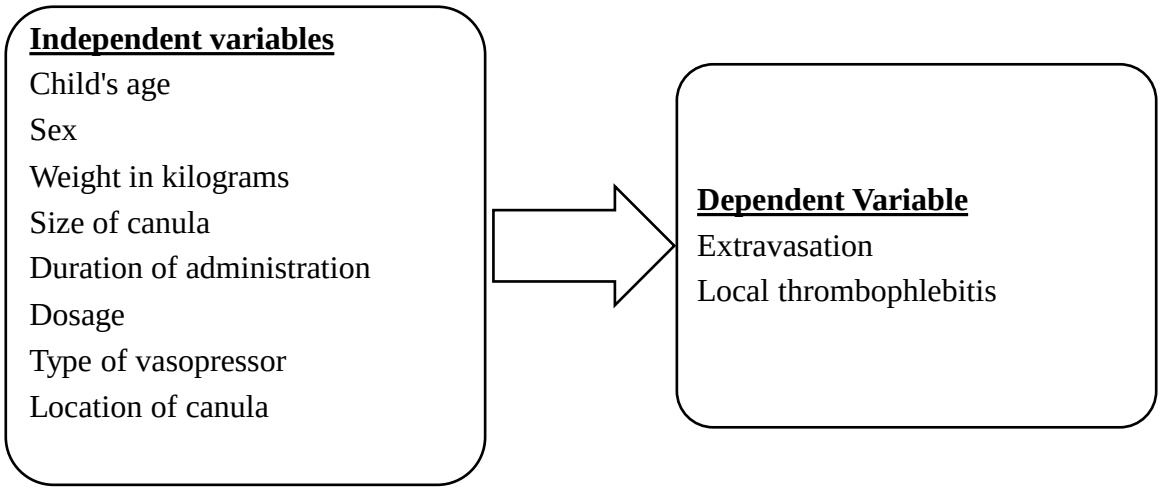


Figure 6: Conceptual framework

Theoretical framework

Evidence from the literature shows that the administration of vasopressors through peripheral access in large doses and over long durations increases the risk of complications (extravasation and local phlebitis). Small cannulas are known to leak and therefore likely to increase the risk of extravasation and local phlebitis. Children's characteristics and types of vasopressors have not been explored in the cited literature. We have therefore conceptualized that younger children may experience local phlebitis more easily than older children due to the nature of their skin. The effect of the type of vasopressor remains unknown and will be assessed in the present study.

2.9 Research Question

What is the safety of peripheral intravenous administration of vasopressors among critically-ill children admitted at KNH?

2.10 Study objectives

Broad objective

To determine the safety of peripheral intravenous administration of vasopressors among critically-ill children admitted at KNH

Specific objectives

- To determine the prevalence of extravasation among critically ill children at KNH who are receiving vasopressors via peripheral lines
- To determine the prevalence of thrombophlebitis among critically ill children at KNH who are receiving vasopressors via peripheral lines

Secondary objective

- To assess for factors (e.g., type of vasopressor, dose, duration of administration and location of the cannula) associated with the development of complications among critically-ill children admitted at KNH receiving vasopressors via PVCs.

CHAPTER 3: METHODOLOGY

3.1 Study design

This was a prospective observational study. The prospective design was chosen to allow us to conduct this study over a period of five months. This design was also suited to our study since our main outcome was the occurrence of complications as a result of peripheral administration of vasopressors.

3.2 Study setting

The study was conducted at Kenyatta National Hospital (KNH) in the paediatric ICU, main ICU and paediatric wards. KNH is the main referral hospital in Kenya. KNH PICU, main ICU and 4B ICU serve the critically-ill children admitted at KNH as well as the referrals from peripheral facilities. PICU accommodates a total of 5 patients while the main ICU admits children when PICU is full. The main ICU is usually for adult patients but admits paediatric patients when they have space and PICU is full. The common conditions managed are septic shock, hypovolemic shock, respiratory diseases, cardiac conditions, and muscular diseases among others.

3.3 Study period

The study was conducted over a period of five months.

3.4 Study population

The study population was paediatric patients aged 1 month to 12 years. These were children requiring vasopressor support.

Inclusion criteria

Critically ill children admitted to paediatric ICU, main ICU and wards and getting vasopressors via peripheral lines.

Children whose parents/guardians consented to participation

Children whose parents/guardians gave permission after the child had assented to participate in the study

Exclusion criteria

Critically-ill children not requiring vasopressor support

Children whose parents decline consent or children who decline assent

Children with skin conditions that may have impeded accurate assessment

Neonates

3.5 Sampling Method

Due to the low bed capacity to accommodate paedtiatric patients in the ICUs, this study employed consecutive sampling. Patients were recruited into the study until the desired sample was reached.

3.6 Sample size calculation

Cochran's Sample Size Formula

$$n = Z^2_{\frac{\alpha}{2}} * \frac{p(1-p)}{d^2}$$

Where:

d is the preferred level of precision (i.e., the margin of error), 0.1

p is the proportion with extravasation from past studies, 0.15 according to (6)

$n = 1.96^2 * 0.15 * 0.85/0.1^2$

n = 49

3.7 Recruitment and consenting procedures

Recruitment and consenting of potential study participants began after the study had been approved. We screened patients for eligibility once a patient was started on inotropic support via a peripheral line at any point after admission. Once the patient qualified to be part of the study, we then approached the parent for signed consent for the child to participate in the study. Parents who decline consent had their children exempted from the study.

3.8 Study variables

Independent variables

Child's age

Sex

Size of canula

Location of canula

Duration of administration

Dosage

Type of vasopressor

Dependent variables

Extravasation

Thrombophlebitis

3.9 Study procedures

The principal investigator employed one research assistant to assist with data collection. The research assistant was trained in seeking consent and how to use the data collection tool.

Once the study had been approved by the Kenyatta National Hospital/University of Nairobi ethics review committee, we conducted a pilot study in the main ICU at Mama Lucy Kibaki Hospital using 10% of the questionnaires. This helped in determining the validity of the questionnaire.

After recruitment, we monitored the patients for the development of any complications. Patients exited the study once the outcome of interest was observed. The outcomes of interest (extravasation and thrombophlebitis) were determined entirely through evaluation by the principal investigator and the research assistant using an infiltration and extravasation scale (Appendix III). The complications that arose were notified to the attending doctors for action. Once data collection was complete, we proceeded to data management and analysis.

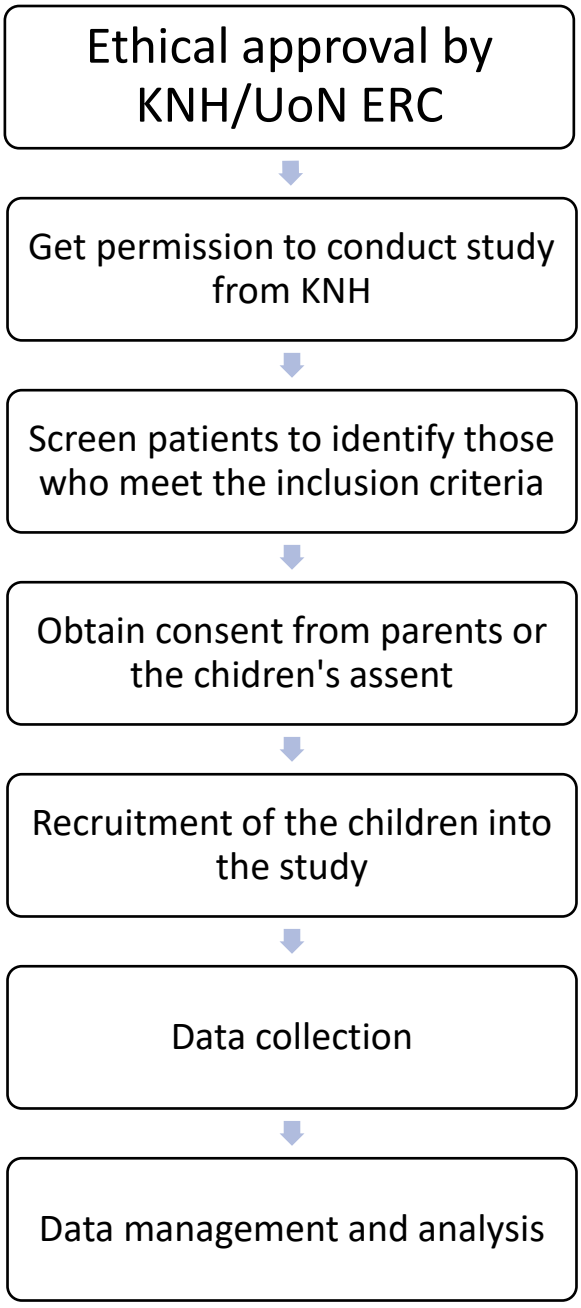


Figure 7: Study procedure flow chart

3.8 Data management and analysis

Data management

The filled questionnaires were checked for completeness and more responses sought if not complete. The questionnaire responses were then coded and entered into excel. For quality control, each tenth observation in excel was compared with the hard copy responses to check

entry errors. The data was stored in a password-protected computer. This data was also stored in a password-protected hard disk for backup purposes.

The data was then imported into R version 4.0.2 for recoding and cleaning. Data cleaning entailed removing duplicate entries if any and rectifying responses entered under wrong variables.

Data analysis

Continuous variables were summarized using median and interquartile ranges. Categorical variables e.g., gender (male/female), type of vasopressor and presence of extravasation or thrombophlebitis (yes/no) were summarized using frequencies and percentage proportions.

Factors associated with complications of peripheral intravenous administration of vasopressors e.g., the dose of vasopressor and duration of administration on complications (yes/no) were assessed using binary logistic regression. Results were evaluated at 5% significance level using p-values and odds ratios/confidence intervals for odds ratios. P-values less than 0.05 were considered significant, an odds ratio below 1 is a protector, above 1 is a risk factor and 1 has no effect.

3.9 Validity and reliability

For validity, we did a pilot study in the main ICU of Mama Lucy Kibaki Hospital before the actual data collection. The pre-test employed 10% of the sample. This helped in knowing whether the study tool collected the intended data.

The reliability of the questionnaire was tested using Cronbach's alpha based on the pre-test data. Cronbach's alpha value of 0.6 and above was considered reliable.

ETHICAL CONSIDERATIONS

Permission to conduct the study was sought from KNH/UON Research and Ethics Committee. The involvement of respondents was by choice; removal of oneself from the study was allowed at any point. The anonymity of the participants was ensured by coding the observations. No use of names or subject identifiers. The cost of the study was not transferred to the respondents. Study results were availed to the KNH/UON Ethics and Research Committee and the UON

Department of Paediatrics. Data collection was carried out only after the acceptance of a formal request to collect data by the KNH Research and Programs Department.

CHAPTER 4: STUDY RESULTS

Characteristics of study participants

This section describes the study participants at admission. Of the 49 children, 31 (63.3%) were male and the rest were female. With respect to the individual units, there were 28 study participants were recruited from the paediatric ICU of which 18 (64.3%) were males. Of the 15 participants recruited from main ICU, 9 (60%) were male while 6 participants were recruited from the wards where 4 (67%) were male.

In terms of age, the median overall age was 21 months with an interquartile range (IQR) of 10 to 28 months. With respect to the individual units, the median age for PICU participants was 19 months (IQR 9, 27), main ICU median age was 20 months (IQR 13, 26) and in the wards, the median age was 21 months (IQR 21, 29) months.

Table 3: Characteristics of study participants (N = 49)

			Source of patient		
			PICU N = 28	**Main ICU N = 15**	**Wards N = 6**
Characteristic	**Description**	**N (%)**	**n (%)**	**n (%)**	**n (%)**
Gender	Female	18 (36.7)	10 (35.7)	6 (40)	2 (33)
	Male	31 (63.3)	18 (64.3)	9 (60)	4 (67)
Age in months	Median (IQR)	21 (10, 28)	19 (9, 27)	20 (13, 26)	21 (21, 29)
Age in years	Range	0.2, 9			
Diagnosis at admission	Septic shock	48 (98)	27 (96)	15 (100)	6 (100)
	CVST	1 (2)	1 (4)		

***IQR**-interquartile range, **CVST**-cerebral venous sinus thrombosis*

In terms of the diagnosis at admission, 48 (98%) of the participants had septic shock and the remaining had cerebral venous sinus thrombosis. With respect to the individual units, 27 (96%) of the participants from PICU had septic shock, all the 15 participants from main ICU had septic shock and equally all the participants from the wards had septic shock (Table 3).

Information on inotropic management of the study participants

This section presents inotropic management of the study participants. These includes the site of the cannula, size of the cannula, inotropes used, their doses and the duration.

Of the 49 participants, 19 (38.8%) had the cannulas in the hands, 14 (28.6%) in the external jugular and the rest in the scalp veins. Of the 28 participants from PICU, 10 (35.7%) had the cannulas in the hands, 7 (25%) had cannulas in the external jugular veins and the rest in the scalp. Of the 15 participants from the main ICU, 7 (46.7%) had cannulas in the hands, 3 (20%) had cannulas in the external jugular veins and the rest in the scalp veins. There were 6 participants from the wards of which 4 (66.7%) had cannulas in the external jugular veins and the rest in the hands.

In terms of the median duration of cannula use, the overall median duration of use was 15 hours (IQR 8, 21) hours. In PICU, the median duration of cannula use was 16 hours (IQR 8,21) hours, 10 hours (IQR 7, 20) hours for main ICU and 16 hours (IQR 11, 20) hours for the wards.

Adrenaline was the most used inotrope, 40/49 (81.6%) followed by noradrenaline 14/49 (28.6%) and lastly milrinone 3 out of 49 participants. The rest were combinations. In the respective units, 24 (85.7%) of the participants from PICU used adrenaline, 11 (73.3%) used adrenaline in the main ICU and 5 (83.3%) in the wards. Noradrenaline was used as follows, 8 (28.6%) of participants from PICU, 4 (26.7%) in main ICU and 2 participants in the wards.

The median maximum average dose of adrenaline was 0.1 micrograms/kg (IQR 0.1, 0.15). With respect to the individual units, the median maximum average dose was, 0.1 micrograms/kg (IQR 0.1, 0.15) for PICU, 0.1 micrograms/kg (IQR 0.1, 0.2) in the main ICU and 0.1 micrograms/kg (IQR 0.1, 0.2) in the wards.

The median maximum average dose of noradrenaline was 0.13 (0.1, 0.15). In the individual units, the medium maximum average dose of noradrenaline in micrograms/kg was 0.15 (IQR 0.1, 0.16) in PICU, 0.1 (0.1, 0.1) in the main ICU and 0.15 (IQR 0.13, 0.18) in the wards.

The median duration of adrenaline use in hours was 20 hours (IQR 16, 31) overall. In the individual units, the median duration of adrenaline use in hours was 21 (IQR 16, 35) in PICU, 19 (IQR 16, 24) in the main ICU and 20 (IQR 20, 25) in the wards.

Table 4: Inotropic related clinical management of the study participants

			Source of patient		
		Overall N = 49	**PICU N = 28**	**Main ICU N = 15**	**Wards N = 6**
Characteristic	**Description**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Site of the cannula	Hand	19 (38.8)	10 (35.7)	7 (46.7)	2 (33.3)
	Jugular	14 (28.6)	7 (25)	3 (20)	4 (66.7)
	Scalp	16 (32.6)	11 (39.3)	5 (33.3)	
Gauge of cannula	Gauge 22	10 (20.4)	6 (21.4)	3 (20)	1 (16.7)
	Gauge 24	35 (71.4)	18 (64.3)	12 (80)	5 (83.3)
	Gauge 26	4 (8.2)	4 (14.3)		
Median duration of cannula use in hours	Median (IQR)	15 (8,21)	16 (8, 21)	10 (7, 20)	16 (11,20)
Inotropes used	Adrenaline	40 (81.6)	24 (85.7)	11 (73.3)	5 (83.3)
	Noradrenaline	14 (28.6)	8 (28.6)	4 (26.7)	2
	Milrinone	3	2		1
	Adrenaline/ noradrenaline	5 (10.2)	4		1
	Adrenaline/ milrinone	2	2		
	Noradrenaline/ milrinone	1			1
Average dose of adrenaline	Median (IQR)	0.1 (0.1, 0.15)	0.1 (0.1, 0.15)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)
Average dose of noradrenaline	Median (IQR)	0.13 (0.1, 0.15)	0.15 (0.1, 0.16)	0.1 (0.1, 0.1)	0.15 (0.13, 0.18)
Duration of adrenaline in hours	Median (IQR)	20 (16,31)	21 (16,35)	19 (16, 24)	20 (20, 25)
Duration of noradrenaline in hours	Median (IQR)	43 (28, 68)	36 (25,38)	74 (58, 78)	
Co-administered drugs	Calcium gluconate	10 (20.4)	6 (21.4)	3	1
	Potassium chloride	13 (26.5)	10 (35.7)	2	1
	Calcium gluconate/potassium chloride	13 (26.5)	5 (20.8)	5	3
	Calcium gluconate/potassium chloride /Phenytoin	2 (4)	2		
	None	13 (22)	7	5	1

The overall median duration of noradrenaline use in hours was 43 (IQR 28, 68). In the individual units, the median duration of noradrenaline use was 36 (25, 38) in PICU and 74 (58, 78) in the main ICU (Table 4).

Complications of administering inotropes via peripheral lines

Two complications of administering inotropes via peripheral lines were encountered in the study participants. These were extravasation and thrombophlebitis. Overall, 33 (67.3%) of the children developed extravasation and 7 (14.3%) developed thrombophlebitis. In the specific units, 19 (67.9%) developed extravasation in PICU, 10 (66.7%) in the main ICU and four in the wards. With respect to thrombophlebitis, three were in PICU, two in the main ICU and two in the wards.

Table 5: Complications of administering inotropes via peripheral lines

			Source of patient		
		Overall N= 49	**PICU N = 28**	**Main ICU N = 15**	**Wards N = 6**
Characteristic	**Description**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Complications	Limb necrosis	Did not occur			
	Tissue ischemia	Did not occur			
	Extravasation	33 (67.3)	19 (67.9)	10 (66.7)	4
	Thrombophlebitis	2	1	2	
Grade of extravasation N = 33	Grade 1	25 (75.8)	14 (73.7)	7	4
	Grade 2	8 (24.2)	5	3	
Site of extravasation N = 33	Hand	16 (48.5)	11	2	3
	Jugular	6 (18.2)	3	2	1
	Scalp	14 (42.4)	6	8	

The majority of the study participants 25 (75.8%) had grade 1 extravasation and 8 (24.2%) had grade 2. The rest did not have extravasation. In the respective units, 14 (73.7%) of the participants in PICU had grade 1 extravasation and five had grade 2. In the main ICU, seven participants had grade 1 extravasation and three had grade 2 extravasation. Four participants

from the wards had grade 1 extravasation. In terms of the site of extravasation, 16 (48.5%) occurred in the hands, 14 (42.4%) occurred in the scalp veins and the rest in the external jugular veins.

Prevalence of extravasation among children receiving inotropes via peripheral lines

A total of 33 out of 49 children developed extravasation. Therefore, the prevalence of extravasation in this study was 67% (95% CI 52%, 80%) Figure 8.

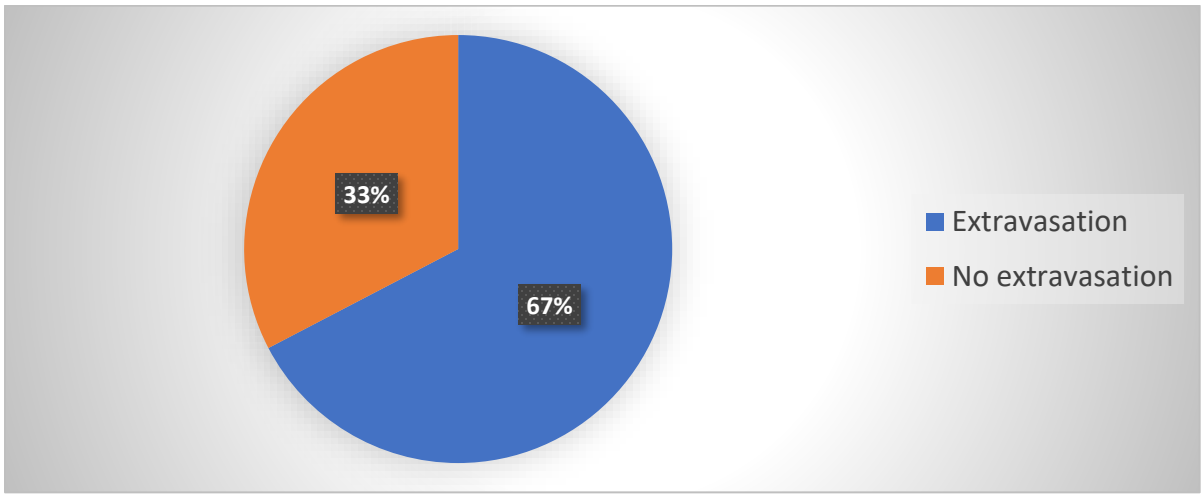


Figure 8: Prevalence of extravasation

Prevalence of thrombophlebitis among children receiving inotropes via peripheral lines

A total of 2 out of 49 children developed thrombophlebitis. This translated to a prevalence of 4% (95% CI 1%, 15%) Figure 9.

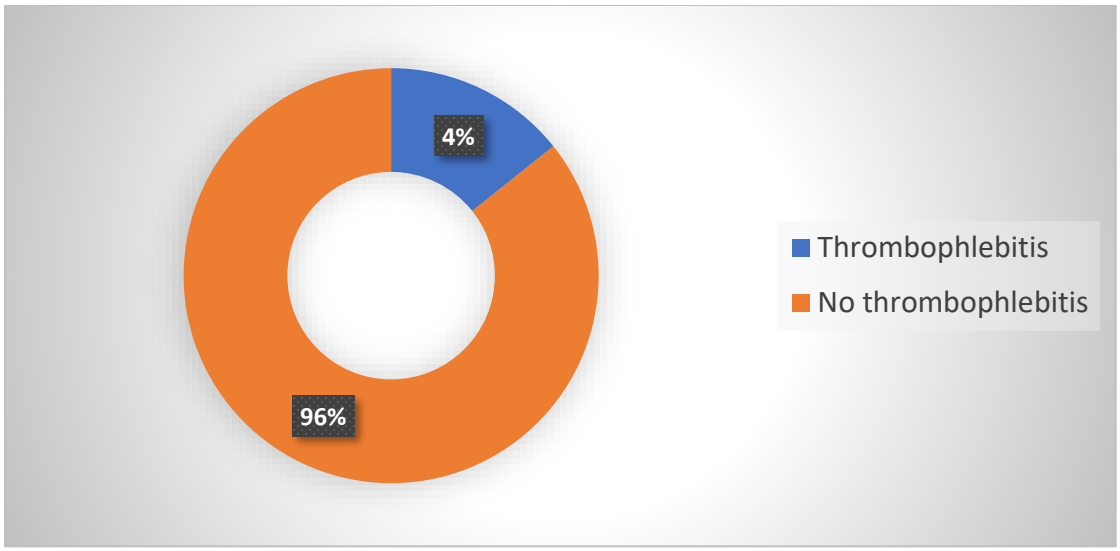


Figure 9: Prevalence of thrombophlebitis.

Overall prevalence of acute complications of peripheral administration of vasopressors

Overall, there were 34 children with acute complications of peripheral administration of vasopressors. These included 32 children with extravasation alone, 1 child with extravasation and thrombophlebitis combined and one child with thrombophlebitis alone. The overall prevalence of complications was 69.4% (95% CI 54.4%, 81.3%) Table 6.

Table 6: Overall prevalence of acute complications of peripheral administration of vasopressors (N = 49)

Characteristic	Frequency	%
Extravasation only	32	65.3
Thrombophlebitis only	1	2.0
Extravasation + thrombophlebitis	1	2.0
Overall complications	34	69.4 (95% CI 54.4, 81.3)

Factors associated with the development of complications among critically-ill children receiving inotropes via peripheral lines

Overall, there were 34 children with acute complications of peripheral administration of vasopressors. This included 32 children with extravasation alone, 1 child with extravasation and

thrombophlebitis combined and 1 child with thrombophlebitis alone. The overall prevalence of extravasation was 69.4% (95% CI 54.4%, 81.3%).

Bivariate analysis

The main outcome was complications of administering inotropes via peripheral lines. This outcome was formed from a composite of extravasation and thrombophlebitis. A total of 34 (69%) out of the 49 participants had complications of administering vasopressors via peripheral lines. From the bivariate analysis, the duration of cannula use in hours was significantly associated the development of complications due to infusion of vasopressors via peripheral lines at 5% significance level (p value<0.05).

Table 7: Factors associated with the development of complications among critically-ill children receiving inotropes via peripheral lines

Factor	**Description**	**Complication**			
		Yes N = 34	**No N = 15**	**Crude OR (95% CI)**	**P value**
Age in years	≤2	25	10	1.39 (0.37, 5.18)	0.62
	>2	9	5	***Reference***	
Dose of inotrope	Maximum average dose	NA	NA	0.04 (0.02, 6.34)	0.709
Duration of inotrope	Duration in hours	NA	NA	1.02 (0.97, 1.07)	0.450
Gauge of cannula	Gauge 22	7	3	***Reference***	
	Gauge 24	25	10	1.07 (0.20, 4.76)	0.930
	Gauge 26	2	2	0.43 (0.03, 5.00)	0.486
Duration of cannula	Duration of cannula in hours	NA	Na	1.14 (1.05, 1.27)	0.006
Site of cannula	Jugular	6	8	***Reference***	
	Hand	16	3	7.11 (1.52, 41.97)	0.02
	Scalp	12	4	4.00 (0.89, 20.69)	0.08
Co-administration with other drugs	Yes	24	12	0.6 (0.12, 2.41)	0.49
	No	10	3	***Reference***	

From table 7 above, one hour increase in the use of a cannula increased the risk of developing complications of vasopressor infusion via peripheral lines by 14%, OR 1.14 (95% CI 1.05, 1.27). infusion of vasopressors via cannulas in the hand was significantly associated with the development of complications at 5% significance level compared to using a jugular line (p-

value<0.05). The odds of developing complications given use of hand access to infuse inotropes was 7.11 times more compared to use of external jugular lines, OR 7.11 (95% CI 1.52, 41.97). One hour increase in the infusion of inotropes increased the odds of developing complications by 2%, OR 1.02 (95% CI 0.97, 1.07). The odds of developing complications of peripheral administration of vasopressors for children aged one year and below were 1.38 times the odds of children aged more than one year.

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

Majority of the children developed grade one extravasation followed by those with grade two. A study by Selma et al. revealed that most extravasation injuries that occur in neonates are grade 1 injuries. (41) A search of the literature did not turn up more studies where extravasation injuries have been graded and this observation is already documented in the literature. (42)

This study revealed a high prevalence of extravasation compared to thrombophlebitis. Overall, 34 (69.4%, 95% CI 54.4%, 81.3%) children developed complications of peripheral administration of vasopressors. In terms of individual complications, there were 33 (67%, 95% CI 52%, 80%) children with extravasation and 2 (4%, 95% CI 1%, 7%) children with thrombophlebitis.

Extravasation has been reported in only 3% of children receiving inotropes via peripheral lines. (43) This study does not support our findings and this could be attributed to the age difference in the two studies. While the maximum age in our study was 9 years, the cited study had children up to 18 years old. High incidences of extravasation have been observed in children between 1 year to 12 years compared to those aged 13 to 18 years. (44) In a study conducted by Kumar et al. where children were infused vasopressors via peripheral line under strict monitoring, only 5.9% of the children developed extravasation (9) which is way below our findings. This difference could be attributed to differences in the level of monitoring for complications and changing the intravenous access, when need be, which may not have been done in the current study.

Low levels of extravasation of up to 2.5% have been reported in a similar study (3) while others have reported no extravasation. (45) The extravasations in the current study were mainly grade 1 and 2 and were observed by the study team while extravasation in the referenced study was abstracted from patients' charts which is entirely dependent on the person recording hence high chances of missing lower grades of extravasation. In contrast to paediatric studies, high levels of extravasation of up to 38% have been reported in adults. (46)

While our study shows a high prevalence of extravasation injuries, literature has demonstrated that extravasation injuries among children receiving vasopressors via peripheral lines are low. This may highly be influenced by the person observing and recording the injuries as low grades

of extravasation are likely to be missed. Another possible reason for the high levels of extravasation in our study is that the intravenous access was used for other fluids and drugs other than inotropes and dextrose solutions and potassium chloride have been shown to be responsible for more cases of extravasation than adrenaline. (44)

The levels of thrombophlebitis reported in the current study are supported by literature. (37) Other studies have also reported higher levels than the one reported in our study but still within the reported prevalence. (6)

Our study revealed that the duration cannula use was significantly associated with development of complications of peripheral administration of vasopressors. Longer duration of cannula use was independently associated with the development of complications. No studies were found in the literature to support or dispute our finding. Intravenous access that stays in situ for long may lead to inflammation due to prolonged use with different drugs hence augmenting the risk of extravasation.

We did not find an association between maximum dose of inotrope and the development of complications of vasopressor administration via peripheral lines. This finding is supported by Abrar et al. (3) However, Abrar et al. did find a significant association between the concentration of the inotrope and rate of administration of the inotrope. These components were not included in our study. The later findings by Abrar et al. demonstrate that close monitoring is necessary especially when using higher concentrations of vasopressors.

Though not significant, the current study revealed that children aged two years and below had higher odds of developing complications of peripheral administration of vasopressors compared to children age 2 years and above. This is consistent with literature where younger children have been reported to be susceptible to extravasation injuries than older children. (41) (47)

Complications of peripheral administration of vasopressors in the current study were more in the upper limbs and the scalp than the jugular veins. The odds of occurrence of the complications in the hands were more than seven times compared to the jugular veins. This finding is consistent with the literature Ghanem et al. who found more cases with extravasation on the upper limbs. (48)

Study strengths

There are no published studies on extravasation injuries among children receiving vasopressors via peripheral lines in Kenya. This is therefore a great start and this study once published will add to the existing international literature from a local point of view

The data was based on primary observation by the study personnel and therefore the veracity of the data is unquestionable.

Study limitations

This is a single-center study. Such studies impede generalization to other centers. We, therefore, recommend future multisite studies of the same kind. The consecutive sampling used here is a non-probabilistic method and therefore limits external validity.

Conclusion

The extravasation injuries that occurred in this study were either grade one or two with the majority being grade one.

The prevalence of extravasation injuries in this study was high and incomparable to most of the findings from the literature.

The prevalence of thrombophlebitis was low and generally within the findings of the published literature.

Only one factor i.e., duration of cannula use was significantly associated with the development of complications of vasopressor administration via peripheral lines in children. Children less than two years, infusion of vasopressors on the upper limbs, smaller cannula gauge had higher odds of developing complications of vasopressor infusions via peripheral lines.

Recommendations

We recommend that larger multisite studies be conducted to ascertain the findings of high prevalence of extravasation injuries and assess the risk factors for the development of complications of vasopressor infusion via peripheral lines.

Peripheral administration of inotropes can continue as per the established guidelines as the complications recorded in this study are non-life threatening and resolves with removal of the cannula.

STUDY TIMELINE

Activity	Nov/Dec. 2022	Jan-March 2023	May-June 2023	July 2023	August 2023
Proposal Development					
Ethical review					
Data collection					
Data analysis and presentation of results					
Final write-up of dissertation					

STUDY BUDGET IN KENYA SHILLINGS

Category	**Remarks**	**Units**	**Unit cost Ksh**	**Total**
	Proposal copies	4	600	2400
	KNH/UON ERC	1	2000	2000
	Hard disk	1	10000	10000
Data collection	Training research assistant	1 day	1500	1500
	Research Assistant	5 months	5000	25,000
Data analysis	Research statistician	1	30000	30000
Dissertation write up	Printing Drafts	5 copies	600	3000
	Printing dissertation	6 copies	600	3600
Contingency				30000
Total				**84,490**

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APPENDIX I: NEXT OF KIN INFORMED CONSENT FORM

Study Title: Safety of Peripheral Intravenous Administration of Vasopressor Agents in Resource-Limited Settings

Principal Investigator/and institutional affiliation: Dr Rukia: Fellow, Department of Paediatrics and Child Health, University of Nairobi

Co-Investigators and institutional affiliation: Dr Rashmi Kumar and DR. Bhupi Reel

Introduction: The above study is being conducted in the paediatric ICU, the main ICU and paediatric wards by the above-listed researchers. The purpose of this consent form is to give you the information you need to decide whether or not your child should participate in the study. You are free to ask questions about the use of the research, the role of your child's participation in the study, the probable risks and benefits, the rights of your child as a volunteer, and anything else that is not clear. After answering all your questions, you may decide if you want your child to participate or not. Once you comprehend and agree for your child to be in the study, you will be requested to sign your name on this form. You should understand the general principles which apply to all participants in medical research: i) Your child's decision to participate is entirely voluntary ii) Your child may withdraw from the study at any time without necessarily giving a reason for his/her withdrawal iii) Refusal to participate in the research will not affect the services your child is entitled to in this health facility or other facilities.

Background

Vasopressors are conventionally administered through a central venous catheter (CVC) though they can also be administered through a peripheral venous catheter. Placement of a CVC requires suitably trained personnel to be on hand, and in resource-limited settings, this requirement may delay placement. In cases where vasopressors are urgently needed, peripheral venous catheters are used for their administration.

Purpose

This study aims to determine the safety of vasopressors administered through a PVC among children admitted to PICU-KNH

Study procedures

The principal investigator will employ one research assistant to assist with data collection. The research assistant will be trained in seeking consent and how to use the data collection questionnaire.

Once the study is approved by the Kenyatta National Hospital/University of Nairobi ethics review committee, we will conduct a pilot study in the main ICU at Mama Lucy Kibaki Hospital using 10% of the questionnaires. This will help in determining the validity of the questionnaire.

We will obtain consent first before data collection. After obtaining consent, we will look for the patients who meet the inclusion criteria. We will then approach the parent/guardian for consent. Once consent is obtained, the patient will be recruited into the study.

The information that we will collect includes; age, sex, where the patient came from, weight in kilograms and the disease that the patient has. We will also document the type of the drug, size of the cannula and duration of administering the drugs. After the preliminary information is recorded, you will be monitored to see if you will develop the outcomes of interest. If the drugs are stopped before you develop the outcomes, we will stop collecting data on you and you will be informed.

Voluntary participation

Your decision for you or your child to participate in this study is voluntary. Once you understand and agree for your child to be in the study, the research personnel will request you to sign your name on this form.

Confidentiality

The data collected will be used solely for this study. We will keep everything you tell us as confidential as possible. We will use a code number to identify your child in a password-protected computer database and will keep all of our paper records in a locked file cabinet.

Benefits

There will be no financial benefit given to your child for participating in this study. Your child's participation will not affect or delay their planned treatment. Also, the information we get from the study will help us better understand the safety of administering vasopressors on peripheral lines. This will help us improve the management of these children better by starting inotropes early through PVCs or by changing to other safer methods of administering vasopressors.

Risk of Participation

We will not alter your child's planned treatment. The observation carried out on your child will not cause any harm.

Right of withdrawal

You may withdraw your child from the study at any time without necessarily giving any reason for the withdrawal. The refusal or withdrawal of your child from this study will not affect the services your child is entitled to, in this health facility or other facilities.

CONSENT FORM (STATEMENT OF CONSENT)

The person being considered for this study is unable to consent for him/herself because he or she is a minor (a person less than 18 years of age). You are being asked to give your permission to include your child in this study.

Parent/guardian statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with the study personnel. I have had my questions answered by him or her in a language that I understand. The risks and benefits have been explained to me. I understand that my participation and that of my child in this study is voluntary and that I may choose to withdraw at any time. I understand that all efforts will be made to keep information regarding me and my child's identity confidential.

Parent/Legal Guardian signature /Thumb stamp: _____ Date __

Parent/Legal Guardian printed name: _____

Assenting Form

I ……as a parent/guardian…… ……hereby permit the child's participation in the prospective observational study assessing the Safety of Peripheral Intravenous Administration of Vasopressor Agents in Resource-Limited Settings at KNH, the child has understood the purpose of the study and assented to participate.

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given his/her consent.

Printed Name: _____ Date: _____ Signature:

In case you have any questions concerning the study, feel free to contact the following persons during official working hours:

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KIAMBATISHO I: FOMU INAYOFUATA YA RIDHAA YA JAMAA

Kichwa cha Somo: Usalama wa Mishipa ya Pembeni inapotumika kupeana Vasopressor katika Nch ambazo hasina rasilimali thabithi.

Mpelelezi Mkuu/na uhusiano wa kitaasisi: Dk Rukia Aden: Mwanafunzi, Idara ya Magonjwa ya Watoto na Afya ya Mtoto, Chuo Kikuu cha Nairobi.

Wachunguzi-wenza na uhusiano wa kitaasisi: Dk Rashmi Kumar na DR. Bhupi Reel

Utangulizi: Utafiti hapo juu unafanywa kwa ICU ya watoto, ICU ya watu wazima miongoni mwa watoto waliolazwa humo na Wadi za watoto na watafiti walioorodheshwa hapo juu. Madhumuni ya fomu hii ya idhini ni kukupa taarifa unayohitaji ili kuamua kama mtoto wako ashiriki katika utafiti au la. Uko huru kuuliza maswali kuhusu matumizi ya utafiti, jukumu la ushiriki wa mtoto wako katika utafiti, hatari na manufaa yanayoweza kutokea, haki za mtoto wako kama mtu wa kujitolea, na kitu kingine chochote ambacho hakiko wazi. Baada ya kujibu maswali yako yote, unaweza kuamua ikiwa ungependa mtoto wako ashiriki au la. Ukishaelewa na kukubali mtoto wako awe kwenye utafiti, utaombwa kutia sahihi jina lako kwenye fomu hii. Unapaswa kuelewa kanuni za jumla zinazotumika kwa washiriki wote katika utafiti wa matibabu: i) Uamuzi wa mtoto wako kushiriki ni wa hiari kabisa ii) Mtoto wako anaweza kujiondoa kwenye utafiti wakati wowote bila ya kueleza sababu ya kujiondoa iii) Kukataa. kushiriki katika utafiti hakutaathiri huduma anazostahiki mtoto wako katika kituo hiki cha afya au vituo vingine.

Usuli: Vasopressors hupeanwa kwa kawaida kupitia katheta ya kati ya vena (CVC) ingawa zinaweza pia kupeanwa kupitia katheta ya vena ya pembeni. Uwekaji wa katheta ya vena ya kati unahitaji wafanyikazi waliofunzwa ifaavyo wawepo, na katika nchi isiyo na rasilimali thabithi, hitaji hili linaweza kuchelewesha upangaji. Katika hali ambapo vasopressors zinahitajika haraka, catheter za mishipa ya pembeni hutumiwa kwa uamuzi wao.

Kusudi: Utafiti huu unalenga kubainisha usalama wa vasopressa zinazopeanwa kupitia mishipa ya pempeni miongoni mwa watoto waliolazwa katika chumba cha watu wa hali mahututi, kitengo cha watoto-KNH.

Taratibu za masomo: Mchunguzi mkuu ataajiri msaidizi mmoja wa utafiti ili kusaidia katika ukusanyaji wa data. Msaidizi wa utafiti atafunzwa katika kutafuta ridhaa na jinsi ya kutumia dodoso la kukusanya data. Pindi tu utafiti huo utakapoidhinishwa na kamati ya ukaguzi wa maadili ya Hospitali ya Kitaifa ya Kenyatta/Chuo Kikuu cha Nairobi, tutafanya utafiti wa majaribio katika chumba kikuu cha wagonjwa mahututi katika Hospitali ya Mama Lucy Kibaki

kwa kutumia 10% ya dodoso. Hii itasaidia katika kuamua uhalali wa dodoso. Tutapata kibali kwanza kabla ya kukusanya data. Baada ya kupata kibali, tutatafuta wagonjwa wanaokidhi vigezo vya kujumuishwa. Kisha tutaenda kwa mzazi/mlezi kwa ridhaa. Baada ya kupata kibali, mgonjwa atasajiliwa katika utafiti. Taarifa ambazo tutakusanya ni pamoja na; umri, jinsia, mahali ambapo mgonjwa alitoka, uzito wa kilo na ugonjwa ambao mgonjwa anao. Pia tutaandika aina ya dawa, ukubwa wa kanula na muda wa kupewa dawa. Baada ya maelezo ya awali kurekodiwa, utafuatiliwa ili kuona ikiwa utaendeleza matokeo ya riba. Ikiwa dawa zitasimamishwa kabla ya kupata matokeo, tutaacha kukusanya data juu yako na utafahamishwa.
Kushiriki kwa hiari: Uamuzi wako au mtoto wako kushiriki katika utafiti huu ni wa hiari. Mara tu unapoelewa na kukubali mtoto wako awe katika utafiti, mfanyikazi wa utafiti atakuomba utie sahihi na jina lako kwenye fomu hii.

Usiri: Data iliyokusanywa itatumika kwa utafiti huu pekee. Tutaweka kila kitu unachotuambia kisiri iwezekanavyo. Tutatumia nambari ya msimbo kumtambua mtoto wako katika kuhifadhi data ya kompyuta iliyolindwa na nenosiri na tutaweka rekodi zetu zote za karatasi kwenye kabati ya faili iliyofungwa.

Faida: Hakutakuwa na manufaa ya kifedha atakayopewa mtoto wako kwa kushiriki katika utafiti huu. Ushiriki wa mtoto wako hautaathiri au kucheleweshe matibabu yao yaliyopangwa. Pia, maelezo tunayopata kutoka kwa utafiti yatatusaidia kuelewa vyema usalama wa kupeana vasopressors kwenye mishipa ya pembeni. Hili litatusaidia kuboresha matibabu ya watoto hawa vyema zaidi ama kwa kubadili na kutumia mbinu nyingine salama zaidi za kutoa vasopressors au kuepuka uwekaji wa njia kuu ambazo ni hatari kwa maambukizi.

Hatari ya Kushiriki: Hatutabadilisha matibabu yaliyopangwa ya mtoto wako. Uchunguzi wetu hautaleta madhara yoyote kwa mtoto wako.

Haki ya kujiondoa: Unaweza kumwondoa mtoto wako kwenye utafiti wakati wowote bila kutoa sababunya kujiondoa. Kukataa au kujiondoa kwa mtoto wako katika utafiti huu hakutaathiri huduma anazostahili mtoto wako kupata katika kituo hiki cha afya au vituo vingine.

FOMU YA RIDHAA (TAARIFA YA RIDHAA): Mtu anayezingatiwa kwa ajili ya utafiti huu hawezi kujisimamia kwa sababu yeye ni mtoto mdogo (mtu chini ya miaka 18). Unaombwa kutoa idhini yako ya kujumuisha mtoto wako katika utafiti huu.

Taarifa ya mzazi/mlezi: Nimesoma fomu hii ya idhini au nimesomewa maelezo. Nimepata nafasi ya kujadili utafiti huu na wafanyakazi wa utafiti. Nimejibiwa maswali yangu kwa lugha ninayoielewa. Hatari na faida zimeelezewa kwangu. Ninaelewa kuwa ushiriki wangu na wa mtoto wangu katika utafiti huu ni kwa hiari na kwamba ninaweza kuchagua kujiondoa wakati wowote. Ninaelewa kuwa juhudi zote zitafanywa ili kuweka maelezo kunihusu na ya mtoto wangu kuwa siri.

Saini ya Mzazi/Mlezi wa Kisheria /Muhuri wa kidole gumba: _____Tarehe.....

Jina lililochapishwa la Mzazi/Mlezi: _____

Fomu ya Kuidhinisha

Mimi ……kama mzazi/mlinzi…… wa mgonjwa ninapeana idhini iliyoandikwa kwa ajili ya kushiriki katika utafiti unaotarajiwa wa uchunguzi wa kutathmini Usalama wa kupeana kwa Mishipa ya Pembeni dawa ya Vasopressor katika nchi za jini kiuchumi katika hospitali ya KNH. Hii ni baada ya mgonjwa kuelezewa na kukubali kujumlishwa katika utafiti huu.

Kauli ya mtafiti: Mimi, aliyetia sahihi hapa chini, nimeeleza kikamilifu maelezo muhimu ya utafiti huu kwa mshiriki aliyetajwa hapo juu na ninaamini kuwa mshiriki ameelewa na ametoa ridhaa yake akijua.

Jina Lililochapishwa: _____ Tarehe: _____
Sahihi.....

Iwapo una maswali yoyote kuhusu utafiti, jisikie huru kuwasiliana na watu wafuatao wakati wa saa rasmi za kazi:

MPELELEZI MKUU: Dr Rukia Mohamed Aden

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APPENDIX II: DATA COLLECTION TOOL

Study Identification no. …….

Date…….

Part A: Biodata

1. Ward **a.** PICU **b.** Main ICU **c**. Wards
2. Age of the child in years……..

3. Sex of the child (Male / Female)

Part B: Clinical data

4. Diagnosis …….
5. Blood pressure before starting vasopressors…….
6. Mean arterial pressures before starting vasopressors……..
7. Heart rate before starting vasopressors……..
8. Cold extremities (Yes / No)

Part C: Vasopressor infusion

9. Line site

Line	Site	Gauge	duration
1st line			
2nd line			
3rd line			

10. Type of vasopressor
    a. Adrenaline
    b. Noradrenaline
    c. Milrinone
    d. Dopamine
    e. Dobutamine
11. Dosage infused (maximum dose)

    a……b……c……d……..e……..
12. Duration of vasopressor infusion in hours……..
13. Co-administered drugs
    a. Calcium gluconate
    b. Potassium chloride
    c. Others……..

Part D: Complications of peripheral infusion of vasopressors

14. Tissue necrosis (Yes/No)

15. Limb ischemia (Yes/No)
16. Extravasation (Yes/ No)
17. Grade of extravasation
    a. Grade 0
    b. Grade 1
    c. Grade 2
    d. Grade 3
    e. Grade 4
18. Thrombophlebitis (Yes/No)

APPENDIX III: GRADING OF EXTRAVASATION

Classification of extravasation injuries

Table 8: Infiltration and extravasation scale; from (13)

INS Infiltration and Extravasation Scale

Grade	Clinical Criteria
0	No symptoms
1	Skin blanched
	Edema <1 in (2.5 cm) in any direction
	Cool to touch
	With or without pain
2	Skin blanched
	Edema 1 to 6 in (2.5-15 cm) in any direction
	Cool to touch
	With or without pain
3	Skin blanched, translucent
	Gross edema >6 in (15 cm) in any direction
	Cool to touch
	Mild to moderate pain
	Possible numbness
4	Skin blanched, translucent
	Skin tight, leaking
	Skin discolored, bruised, swollen
	Gross edema >6 in (15 cm) in any direction
	Deep pitting tissue edema
	Circulatory impairment
	Moderate to severe pain
	Infiltration of any amount of blood product, irritant, or vesicant

[a] *Used with permission from Infusion Nurses Society.*[15]

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Ref: KNH-ERC/A/248

19th June, 2023

Dr. Rukia Aden Mohamed
Reg No. H116/4137/2021
Fellow in Paediatric & Critical Care Medicine
Dept. of Paediatric & Child Health
Faculty of Health Sciences
University of Nairobi

19 JUN 2023

Dear Dr. Mohamed,

ETHICAL APPROVAL-RESEARCH PROPOSAL: SAFETY OF PERIPHERAL INTRAVENOUS ADMINISTRATION OF VASOPRESSOR AGENTS IN RESOURCE-LIMITED SETTINGS (P43/01/2023)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P43/01/2023.** The approval period is 19th June 2023 –18th June 2024.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected 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.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. 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.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH- UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
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Safety Of Peripheral Intravenous Administration Of Vasopressor Agents In Resource-Limited Settings

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