RELATIONSHIP BETWEEN HIGH ALERT MEDICATIONS AND A SELECTED OUTCOME AMONG PATIENTS AT INTENSIVE CARE UNITS - CAIRO UNIVERSITY HOSPITALS

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ABSTRACT

Background: Critically ill patients receiving high alert medication are at increased risk for drug –related events; of these is peripheral ischemia. Therefore, they require meticulous assessment for prevention, early detection and management. **This study aimed to** examine the relationship between high alert medications and selected patients' outcome at intensive care units - Cairo University Hospitals. High alert medications in the present study are Vasopressors, and patients' outcome refers to development of peripheral ischemia. **Two research questions were stated:** What is the frequency of peripheral ischemia among critically ill patients receiving high alert medications?; and what is the relationship between severity of peripheral ischemia, medical and demographic characteristics of critically ill patients at a University Hospital – Cairo? **A descriptive exploratory research design** was followed in this study. **A purposive sample** consisting of 120 adult male and female critically ill patients receiving high alert medications (Vasopressors) was included**. Setting:** This study was carried out at two intensive care units affiliated to Cairo University hospitals. **Two tools** were developed by the researchers and utilized to collect data: Patients' demographic and medical data tool; and critically ill patients' assessment tool for development of peripheral ischemia. **Results**: severe peripheral ischemia affected 71.7%, of the studied patients. It was most frequently noticed among patients aged ≥40 years old, males, having septic and cardiogenic shock, having both diabetes and hypertension as comorbidity diseases, smokers and overweight, in percentages of 65.3%, 75%, 70.6%, 54.5%, 84.4%, 74.7% and 77% respectively. Significant statistical relationships were found between demographic, medical characteristics, and severity of ischemia. **Conclusion**: Severe upper and lower peripheral ischemia was a common associated vascular complication among critically ill patients receiving high alert medications (vasopressors) in the present study. **Recommendations**: Meticulous focused and comprehensive assessment is important nursing consideration for critically ill patient receiving vasopressors; Establishment of standardized assessment tools to predict and detect peripheral / limb ischemia among critically ill patients; and replication of the study on a larger probability sample selected from different geographic areas in Egypt.

Key Words: *critically ill patients, high alert medications, vasopressors, patients' outcome, peripheral ischemia*

INTRODUCTION

Critically ill patients represent a unique subset of hospitalized patients. Independent of their diagnosis, and severity of illness, they are at great risk for developing many complications as a result of using multiple drugs, of these are high-risk (high-alert) medications. These medications are a priority issue in patients' safety, however, they may cause significant harm and may lead to death when they incorrectly used or administered (Cohen, Smetzer, Tuohy, & Kilo, In Lopez, Cuervo, Toha, Gonzalez, and Vicedo, 2016). High-alert medications are not only limited to mild

sedatives and opiates, but also include vasoactive drugs which are particularly used to treat hemodynamic instability in the emergency medical management of critically ill patients (Jentzer, et al 2015).

Vasoactive agents function primarily through stimulation of adrenergic receptors or through induction of intracellular processes that mimic sympathetic nervous system end point. They are classically subdivided, based on their predominant pathway of activity into vasopressors and inotropes (Djogovic, 2015,). Vasopressors are powerful drugs used to increase vascular tone, create peripheral vasoconstriction, increase cardiac contractility and systemic vascular resistance (SVR) leading to increased mean arterial blood pressure (MAP), organs perfusion, and cardiac contractility, so improving cardiac output (CO), whereas, inotropes increase myocardial contractility (Bangash, Kong & Pearse, 2015).

Vasopressors are classified into three main groups: catecholamines, smooth muscle, and dopaminergic. The most common catecholamine active medications are epinephrine, norepinephrine, and phenylephrine; and the most common dopaminergic active medication is dopamine. Each of these medications has varying activity on the alpha and beta receptors. Alpha receptors are peripheral vasoconstrictors used to increase SVR. Beta-1 receptors have mostly positive chronotropic (heart rate) and inotropic (contractility) effects on the heart, whereas, Beta-2 receptors act as vasodilators in many organ systems (Van Diepen, 2017).

Despite their widespread clinical use, and well documented life-saving properties, vasopressors can be dangerous and lead to complications if they incorrectly used. Common associated complications include dysrhythmias, myocardial ischemia, hyperglycemia, slow or uneven heartbeat, trouble breathing, and signs of dangerously high blood pressure (including severe headache, blurred vision, confusion, anxiety, chest pain) and signs of anaphylactic reactions In addition, continuous vasopressors infusion can cause peripheral vasoconstriction, numbness, burning, irritation, a cold feeling, and discoloration of the skin "blue lips or fingernails" (Robert, Giradeau & Nremt, 2014, and Marks, 2015).

Decreased perfusion to organs, digits or extremities or anywhere in patients' bodies may play a role in development of peripheral ischemia and development of symmetrical peripheral gangrene (Cox, & Roche, 2015, Ghosh, Bandyopadhyay, & Ghosh, 2010, and Slowikowski & Funk, 2010). Thus, extra vigilance, assessment and close monitoring for signs of inadequate perfusion are required. Anticipation and early detection can help to minimize further damage and determine appropriate preventive strategies. Therefore, the current study was carried out to examine the relationship between high alert medications and selected outcomes among critically ill patients at a University Hospital, Cairo.

SIGNIFICANCE OF THE STUDY

Patients' safety is a component of the Joint Commission's International Patient Safety Goals and Egyptian Hospital Accreditation standards (Egyptian Healthcare Accreditation Organization, 2013). As well, the safety of critical care provision is an essential part of patients' management especially during prescribing, dispensing and administration of high alert medications. This requires studies, practices, and actions promoted to reduce or eliminate the potential risks of unnecessary harm (Aly, Ghoneim & Hassan, 2016).

More specifically, the pharmacodynamics of vasopressors suggests that they may play a role in development of peripheral ischemia. However, very scares researches were carried out in Egypt to examine the effect or the relationship between vasopressors as high alert medications on the outcome of critically ill patients. Therefore, the present study could support the important role of the critical care nurse in ongoing assessment, early detection, and so, prevention of complications associated with high alert medications such as vasopressors.

Through clinical experience, it had been observed that, critically ill patients who are receiving certain vasopressors have alteration in peripheral circulation. Peripheral coldness, cyanosis and skin breakdown were frequently noticed. This raised the researchers' interest to examine the relationship between these high alert medications and development of peripheral ischemia among critically ill patients. Hopefully obtained data could shed the light on complications associated with high alert medications, frequency, and clinical manifestations, so establish base line data that can promote nursing practice and research.

AIM OF THE STUDY

The aim of this study was to examine the relationship between high alert medications and selected patients' outcome, at Intensive Care Units - Cairo University Hospitals.

RESEARCH QUESTIONS

1. What is the frequency of peripheral ischemia among critically ill patients receiving high alert medications at Cairo University Hospital?
2. What is the relationship between severity of peripheral ischemia, medical and demographic characteristics of critically ill patients at Cairo University Hospitals?

SUBJECTS AND METHOD

Research design

A descriptive exploratory research design was followed in this study.

Sample

A purposive sample consisting of 120 adult male and female critically ill patients receiving vasopressors (within the first to second day of starting medications) was included. Patients having a history of peripheral vascular diseases, amputation, and diabetic foot were excluded from the study. The sample size was estimated based on the following formula:

$$n = \frac{N}{1+N\,(e^2)}$$

Where: n - Sample size; N - total population (174); e - margin of error (0.05), at Confidence level = 95%.

Setting

This study was carried out at two intensive care units affiliated to Cairo University hospitals.

Data Collection Tools

Two tools were developed by the researchers and utilized to collect data. These tools are: Patients' demographic and medical data tool and critically ill patients' assessment tool for development of peripheral ischemia. As regards tool (1); "Patients' demographic and medical data sheet"; it covered data such as age, gender, medical diagnosis, duration of ICU stay, laboratory investigations, vital signs, and vasopressors (name, dose, route and duration of administration). The second tool (critically ill patients' assessment form for peripheral ischemia). It involved data about the affected site; skin color, temperature, capillary refill, peripheral pulses, sensation, presence of edema, presence of pain, and presence of other manifestations such as scars, ulcers or hair loss.

Scoring System

One score was allocated for each observed sign, giving a total score of 26, classified as: 15-18 (Mild peripheral ischemia), 18-22 (moderate peripheral ischemia) and 22-26 (severe peripheral ischemia). The higher the assessment scores, the worse limb condition, and severity of ischemia.

Pilot Study

A pilot study was carried out on 12 (10% from total sample size) patients receiving vasopressors to test for relevance, simplicity, clarity, comprehensiveness and applicability of the data collection tools. Carrying out the pilot study gave the researchers experience to deal with the included subjects, and the data collection tools. No modifications were done and the pilot study subjects were included in the study.

Protection of Human Rights

Official permissions were obtained from directors of Intensive Care Units at Cairo university hospitals. As well, written consents were obtained from patients who accepted to be included in the study (or their responsible family member's agreement in case of unconsciousness) after explanation of the nature and purpose of the study. Each patient / relative was free to accept either participate or not, and had the right to withdraw from the study at any time without any rational. As well, patients / relatives were informed that obtained data will not be included in any further researches. Confidentiality and anonymity of each subject were assured through coding of all data.

Procedure

The present study was started by reviewing the related literatures, constructing and preparing data collection tools, obtaining official agreements, assessing for feasibility and availability of the study subjects. After obtaining the official permissions to proceed with the proposed study, actual implementation was initiated by carrying out the pilot study. Actual data collection started on May (2017) by obtaining a list of patients who admitted to the critical care departments and met the inclusion criteria. Then patients / responsible family members who agreed to participate in the study were interviewed individually to explain the nature and purpose of the study. Then they were asked to sign out the written consents. The researchers completed patients' demographic and medical data sheet (tool 1). Patients' files were used to obtain the needed data.

BMI was estimated according the British Association for Parenteral and Enteral Nutrition (BAPEN's) guidelines (2011), by measuring mid upper arm circumference (MUAC). BMI was classified as: underweight (MUAC is < 23.5 cm); overweight (MUAC is > 32.0 cm); and within normal BMI (MUAC values in 23.5-32 cm). Then, base line assessment of limbs was done using tool (2). Assessment was carried out for patients' upper and lower limbs on daily basis until the medications were discontinued, or the patient was discharged. Inspection of for skin color, temperature, capillary refill was done, in addition to palpation of peripheral pulses. Then the researchers documented the assessment data. This assessment required approximately 25 minutes per patient.

Statistical Analysis

The collected data were coded, organized, categorized and statistically analyzed using the statistical package for social science (SPSS) version (20). The appropriate statistical analysis was done using descriptive and inferential statistics.

RESEARCH RESULTS

Figure 1 clarifies that the entire studied sample had peripheral ischemia, with the highest frequency for severe stage (71.7%), with a total mean assessment score of 22.8+SD=2.21.

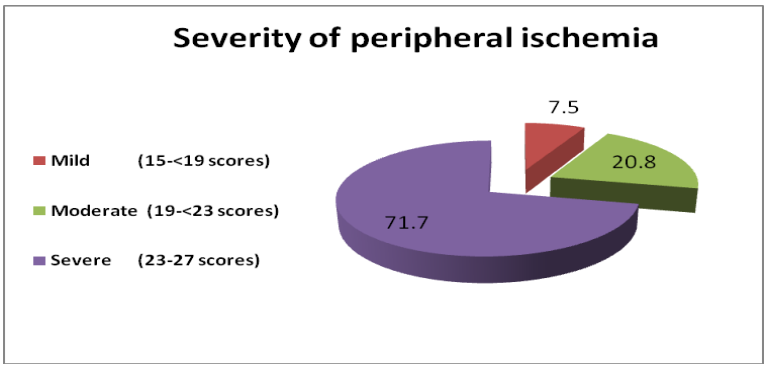

Figure 1: Severity of Peripheral Ischemia among the Studied Sample, (N=120)

Figure 2 shows that most of the studied sample had peripheral ischemia in upper and lower extremities. Right and left lower limb ischemia was found in percentages of 83.3% and 80.8% respectively. However, right and left upper limb ischemia were found among nearly half of the studied sample, in percentage of 45% and 40.8% respectively.

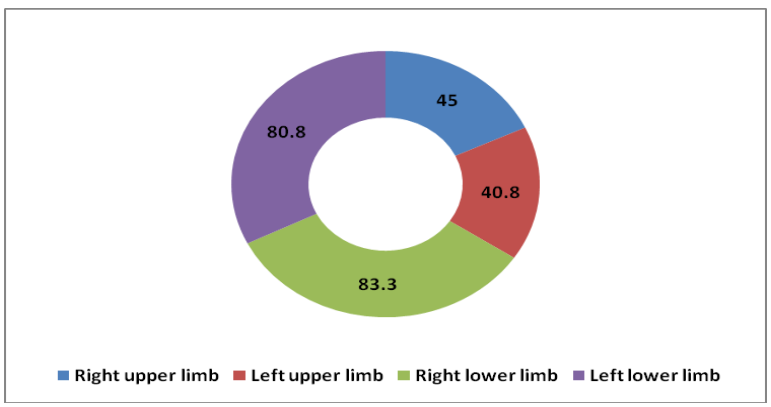

Figure 2: Site of Peripheral Ischemia among the Studied Sample, (N=120)

Figure 3 shows that, delayed capillary refilling time, coldness, reduced/ absent sensation, and edema were the most frequently noticed manifestations of peripheral ischemia among the studied sample, in percentages of 100%, 100%, 95%, and 85% respectively.

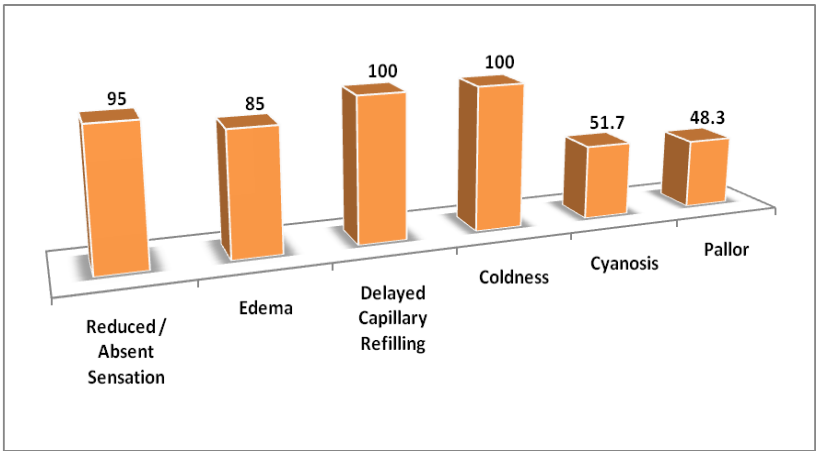

Figure 3: Manifestations of Peripheral Ischemic among the Studied Sample (N= 120)

Figure 4 shows that peripheral pulses were very weak in the right and left lower and upper limbs in percentage of 70.8%, 69.2%, 37.5% and 33.3% respectively, and it was absent among 13.3%, 12.5%, 7.5% and 7.5% respectively.

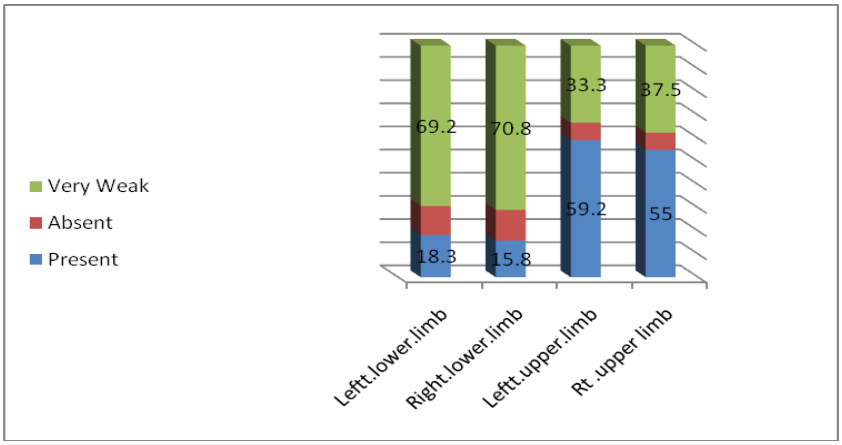

Figure 4: Peripheral pulses in upper and lower extremities of the studied sample (N-120)

Relationship between severity of Peripheral Ischemia, Medical and Demographic Characteristics

Table 1 shows that, cumulatively 66.7.8% of the studied sample was in the age group of 40 - 60 years, with a mean age of 53.92 ± 12.12. Most (80%) of patients received both epinephrine and norepinephrine (at the same time). High doses of epinephrine (More than 0.09mic/kg/min), norepinephrine (more than 0.3mic/kg/min) and dobutamine (more than10 mic/kg/min) were administered to the great majority of patients (85.8%). The mean duration of receiving vasopressors of 19.33± SD= 7.22. No significant statistical relationship was found between age and vasopressor name/ type.

Table 1: Relationship between Age and Vasopressors among the Studied Sample (N=120)

Age Categories		Vasopressors Norepinephrine	Epinephrine & Nor-epinephrine	Norepinephrine & Dobutamine	Total
30-	N (%)	0 (0.0%)	10 (8.3%)	(1.7%)	12 (10.0%)
40-	N (%)	0(0.0%)	30 (25.0%)	(5.0%)	36 (30.0%)
50-	N (%)	1(0.8%)	35 (29.2%)	(6.7%)	44 (36.7%)
≥60	N (%)	1(0.8%)	22 (18.3%)	(4.2%)	28 (23.3%)
Total	N (%)	2 (1.7%)	97 (80.8%)	1(17.5%)	120 (100%)
Chi square: 1.603 P≤ 0.952 (NS)					

Table 2 shows that, severe peripheral ischemia was most frequently noticed among patients in the age group of 40 – 50 (n=22/36=61.11%); 50-60 (n=30/44=68.2%); and more than 60 years old (n=27/28=96.4%), representing a cumulative number of n=79/65.3% of the total sample. A significant statistical relationship was found between age and severity of peripheral ischemia (Chi square: 12.768, p< 0.05).

Tale 2: Relationship between Age and Severity of Peripheral Ischemia among the Studied Sample (N=120)

Age Categories		Severity of Peripheral Ischemia Mild (15-19score)	Moderate (19-23 score)	Severe (23-27 score)	Total
30-	N (%)	2 (1.7%)	3 (2.5%)	7 (5.8%)	12 (10%)
40-	N (%)	3 (2.5%)	11 (9.2%)	22 (18.3%)	36 (30.0%)
50-	N (%)	4 (3.3%)	10 (8.3%)	30 (25.0%)	44 (36.7%)
≥ 60	N (%)	0 (0.0%)	1 (0.8%)	27(22.5%)	28 (23.3%)
Total	N (%)	9 (7.5%)	25 (20.8%)	86 (71.7%)	120 (100%)
Chi square: 12.768, p< 0.05					

As shown from table 3, around three quarters (73.3%) of the studied sample was males; more than half of this group (n=66 / 55%) had severe peripheral ischemia representing 75% of male patients. Moderate peripheral ischemia was noticed among nearly a quarter (n=20/22.7 %) of male patients. There was a significant statistical relationship between severity of peripheral ischemia and gender.

Table 3: Relationship between Gender and Severity of Peripheral Ischemia among the Studied Sample, (N= 120)

Gender		Severity of Peripheral Ischemia Mild (15-19 score)	Moderate (19-23score)	Severe (23-27 score)	Total
Male	N (%)	2 (1.7%)	20 (16.7%)	66 (55%)	88 (73.3%)
Female	N (%)	7 (5.58%)	5 (4.2%)	20 (16.7%)	32 (26.7%)
Total	N (%)	9 (7.5%)	25 (20.8%)	86 (71.7%)	120 (100%)
Chi square test value: 13.1, p≤ 0.001					

Table 4 shows that nearly half of patients (N= 56/46.6%) had shock (septic and cardiogenic). Severe peripheral ischemia was frequently noticed among patients with septic shock (n= 24/ 34 = 70.6%) and cardiogenic shock (n=12 /22 = 54.5%). No significant statistical relationship was found between diagnosis and severity of peripheral ischemia.

Table 4: Relationship between Diagnosis and Severity of Peripheral Ischemia among the Studied Sample, (N- 120)

Diagnosis		Severity of Peripheral Ischemia			Total
		Mild (15-19score)	Moderate (19-23 score)	Severe (23-27 score)	
Septic Shock	N (%)	4 (3.3%)	6 (5.0%)	24 (20.0%)	34 (28.3%)
Cardiogenic Shock	N (%)	2 (1.7%)	8 (6.7%)	12 (10.0%)	22 (18.3%)
Cardiovascular disorders	N (%)	2 (1.7%)	5 (4.2%)	10 (8.3%)	17 (14.2%)
Respiratory disorders	N (%)	1 (0.8%)	2 (1.7%)	12 (10 %)	15 (12.5%)
GIT disorders	N (%)	0 (0.0%)	1 (0.8%)	15 (12.5%)	16 (13.3%)
Neurologic disorders	N (%)	0 (0.0%)	3 (2.5%)	13 (10.8%)	16 (13.3%)
Total	N (%)	9 (7.5%)	25 (20.8%)	86 (71.7%)	120 (100%)
Chi square: 11.846, p≤ 0.296					

Table 5 shows that both diabetes and hypertension are the most frequent co-morbid diseases among more than half (53.3%) of the studied sample; most of this group (n= 54/64= 84.4%) had severe peripheral ischemia. A significant statistical relationship was found between co-morbidity diseases and severity of peripheral ischemia (Chi square = 13.546, P≤0.015).

Table 5: Relationship between Co-morbidity Diseases and Severity of Peripheral Ischemia among the Studied Sample, (N- 120)

Co-morbidities		Severity of Peripheral Ischemia			Total
		Mild (15-19score)	Moderate (19-23 score)	Sever (23-27 score)	
No co-morbidities	N (%)	1 (0.8%)	4 (3.3%)	3 (2.5%)	8 (6.7%)
Diabetes	N (%)	4 (3.3%)	9 (7.5%)	20 (16.7%)	33 (27.5%)
Hypertension	N (%)	1 (0.8%)	5 (4.2%)	9 (7.5%)	15 (12.5%)
Diabetic and Hypertension	N (%)	3 (2.5%)	7 (5.8%)	54 (45.0%)	64 (53.3%)
Total	N (%)	9 (7.5%)	25(20.8%)	86 (71.7%)	120 (100%)
Chi square: Chi square: 13.546 , P≤0.015					

Table 6 shows that more than two thirds (n=77/64.2%) of the studied sample was overweight (BMI 25-29.9 kg/ squared meter), of these, n=59 (77%) had severe peripheral ischemia. A significant statistical relationship was found between BMI and severity of peripheral ischemia (Chi square: 10.17, P≤0.038).

Table 6: Relationship between Body Mass Index (BMI) and Severity of Peripheral Ischemia among the Studied sample (N= 120)

BMI Category		Severity of Peripheral Ischemia Mild (15-19score)	Moderate (19-23 score)	Severe (23-27 score)	Total
Within normal BMI	N (%)	3(2.5%)	10 (8.3%)	12 (10.0%)	25 (20.8%)
Over weight	N (%)	6(5.0%)	12 (10.0%)	59 (49.2%)	77 (64.2%)
Obese	N (%)	0 (0.0%)	3(2.5%)	15 (12.5%)	18 (15 %)
Total	N (%)	9 (7.5%)	25(20.8%)	86 (71.7%)	120 (100%)
Chi square: Chi square: 10.17, P≤0.038					

Table 7 shows that around three quarters (n=87/72.5%) of the studied sample were smokers, of these n=65/74.7% (representing 54.2% of the total studied sample) had severe peripheral ischemia. A high significant statistical relationship was found between smoking and severity of ischemia (Chi square=12.53, P≤0.002).

Table 7: Relationship between Smoking and severity of Peripheral Ischemia among the Studied sample, (N= 120)

Smoking habit		Severity of Peripheral Ischemia Mild (15-19score)	Moderate (19-23 score)	Severe (23-27 score)	Total
Non smokers	N (%)	7 (5.8%)	5 (4.2%)	21 (17.5%)	33 (27.5%)
Smokers	N (%)	2 (1.7%)	20 (16.7%)	65 (54.2%)	87 (72.5%)
Total	N (%)	9 (7.5%)	25(20.8%)	86 (71.7%)	120 (100%)
Chi square: Chi square: 12.53 P≤0.002					

DISCUSSION

Critically ill patients are at high risk for actual or potential life threatening health problems not only because of the disease itself, but also as a result of receiving high alert medications which in one hand may be life saving, and on the other hand lead to undesired effects. Among these medications are vasopressors. Patients in the present study were examined throughout their ICU stay once vasopressors were commenced in attempt to achieve the aim of examining the relationship between high alert medications and a selected patients' outcome which is peripheral ischemia. To achieve this aim, two research questions were stated; the first research question was concerned with frequency of peripheral ischemia among the studied sample and the second was question addressed the relationship between severity of peripheral ischemia, medical and demographic characteristics. The following represents interpretation and elaboration of findings obtained from this study in attempt to provide the answer for the stated research questions.

As regards frequency of peripheral ischemia, the present study showed that severe peripheral ischemia was found among nearly three quarters of the studied sample. It affected both the upper and lower extremities, and it was manifested by very weak peripheral pulses, delayed capillary refilling time, coldness, reduced / absent sensation and edema. In this regards Wang, Kim, & Kashyap (2016) described acute limb ischemia as one of the most common vascular emergencies, with high risk for limb loss if it is not treated expediently. It is a sudden loss of

limb perfusion and the presence of symptoms within 14 days of onset. It almost always presents with limb pain. Further symptoms include pallor and coldness in the affected extremity.

Acute peripheral /limb ischemia may be caused by many factors such as acute thrombosis of a limb artery, bypass grafts, or a diseased artery, dissection, and/or trauma of the peripheral arteries and specific medications administration such as vasopressors (Creager, Kaufman & Conte, 2012). This is of special concern especially where all the studied sample received vasopressors and the mean duration of receiving vasopressors by the present study sample was 19.33+ SD= 7.22, reflecting prolonged duration of administration, so high susceptibility to ischemia. Vasopressors at by increasing Cardiac Output and Systemic Vascular Resistance through increasing contractility and heart rate as well as inducing peripheral vasoconstriction, and so reduction of blood flow (van Diepen, etal., 2017). When imbalance between the needs of the peripheral tissues and the blood supply occurs, acute ischemia develops (Chiu & Chien, 2011). As ischemia progresses, stagnant blood coagulates leading to mottling that is darker in color, coarser in pattern, and does not blanch. Finally, large patches of fixed staining progress to blistering and liquefaction. It is considered an emergency and needs treatment (Patlola & Walker, 2015).

Signs and symptoms of ischemia depend upon how quickly the blood flow is interrupted and where it occurs. They can be described using the 6 Ps: Pain / "rest pain" (the early symptoms of ischemia); Pallor; paralysis; paresthesia; pulse deficit; and poikilothermia (inability to maintain a constant core temperature). Other manifestations include open sores, non-healing wounds, thickening of the toenails, edema, impaired capillary refill, necrosis and gangrene (Novo, Coppola & Milio, 2017). Therefore, accurate ongoing assessment of patients receiving vasopressors is an important responsibility for the critical care nurse who must have the ability to interpret and integrate assessment data in patients' management.

Examining the relationship between severity of peripheral ischemia, medical and demographic characteristics

Severity of peripheral ischemia in the present study was significantly related to gender and age. Nearly three quarters of male patients had severe peripheral ischemia and the other quarter had moderate ischemia. It occurred among old adults in the age group of 40 years old and more. In this regards Ortmann, Nüesch, Traupe, Diehm, & Baumgartner,(2012) were in agreement with the present study findings and indicated that gender is an independent risk factor for distribution pattern and lesion morphology in limb ischemia and they found that severe peripheral limb ischemia is very common among older adult males. As well, Kuukasjärvi & Salenius, (2015) showed agreement with the current study finding, they studied "peri-operative outcome of acute lower limb ischemia", and reported that males were affected more than females. In addition, Ciocan, et al, (2017) examined pattern of patients with limb ischemia and reported high frequency among male patients. In contrast, Nehler, et al., (2014) studied the epidemiology of peripheral arterial disease and critical limb ischemia and revealed that severe limb ischemia more frequent among females and old adults.

As regards medical diagnosis, shock (Septic and cardiogenic shock) was the medical diagnosis among more than two thirds of the studied sample. In this regards De Backer, (2017) mentioned

that shock is a life threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells. The circulation is unable to deliver sufficient oxygen to meet the demands of the tissues, resulting in cellular dysoxia (inadequate tissue oxygenation). It is also associated with signs of impaired tissue perfusion such as skin vasoconstriction or mottling, acrocyanosis, impaired capillary refill time, impaired microcirculation. This could reflect the worse condition of the studied sample. However, no significant statistical relation was found between diagnosis and severity of peripheral ischemia.

Diabetes and hypertension were the most frequent comorbidity diseases among more than half of the studied sample, with a significant statistical relation to severity of ischemia. Diabetes is one of the major risk factors for developing peripheral /limb ischemia. It increases the severity of ischemia and lead to poor prognosis (Dick, et al., 2017). As well, arterial hypertension was reported as a major risk factor for lower-extremity occlusive disease (Faglia, et al., 2016). A significant statistical relation between severity of limb ischemia and hypertension was reported by Davies, (2012). The patients' condition becomes worse when diabetes is associated with hypertension which may predispose to peripheral arteries occlusion, and so increased severity of ischemia.

Most of the studied patients received high doses of both epinephrine (More than 0.09 mic/kg/min) and norepinephrine (more than 0.3 mic/kg/min) at the same time, with no significant statistical relationship between the dose, medical diagnosis, and demographic characteristics. Epinephrine is an endogenous catecholamine that has many therapeutic applications. Endogenous epinephrine is produced primarily from norepinephrine in the adrenal medulla. It has complex target organ effects. It is a potent agonist at both alpha- and beta-receptors throughout the body except for the sweat glands and facial arteries. Epinephrine is a nonselective adrenergic agonist; it stimulates alpha1, alpha2, beta1, and beta2 adrenergic receptors. Stimulation of alpha1-receptors leads to arteriolar vasoconstriction, and stimulation of beta1-receptors induces a positive chronotropic and inotropic effects. Stimulation of beta2-receptors leads to arteriolar vasodilatation, bronchial smooth muscle relaxation, and increased glycogenolysis (Sachdeva, 2014).

Norepinephrine is an especially powerful vasoconstrictor hormone and inotrope. It is recommended as the first-line vasopressor in septic shock. It acts on alpha-adrenergic receptors to produce constriction of resistance and capacitance vessels, thereby increasing systemic blood pressure and coronary artery blood flow. It also acts on beta1-receptors producing positive chronotropic and inotropic effects. Relatively with lower doses, norepinephrine produces cardiac-stimulant effect, however, with larger doses it acts as vasoconstrictor (Paige, 2015). Hemodynamic consequences of norepinephrine are increased systolic, and diastolic, pulse pressures, cardiac output and total peripheral resistance (Gordon & Russell 2012). In this regards, Stratton, Berlin, & Arbo, (2017) conducted a study about the use of vasopressors and inotropes in sepsis, and revealed that, most vasoactive agents such as epinephrine and norepinephrine increase cardiac contractility and produce vasoconstriction, so predispose to peripheral ischemic changes.

Based on understanding the mechanism of action of the commonly administered vasopressors among the studied sample, one can admit why the entire studied sample had different degrees of

peripheral ischemia ranging from mild to severe. This is of special concern especially where the mean duration of receiving vasopressors was19.33+SD= 7.22. Prolonged administration of norepinephrine as mentioned by Cohen, (2015) may result in volume depletion which if not continuously corrected may lead to hypotension upon discontinuation of norepinephrine, visceral vasoconstriction, and lactic acidosis. In addition, drug-induced sever vasoconstriction may progress to severe tissue hypoxia ischemic injury and gangrene.

The present study revealed that, around three quarters of the involved sample were smokers and most of these patients had severe peripheral ischemia. A significant statistical relationship was found between smoking and severity of ischemia. In this regards Farber & Eberhardt, (2016) indicated that smoking is the most preventable risk factor for the development of peripheral artery diseases. It dramatically increases the risk of progression to sever limb ischemia. As well, Davies, (2012) found cigarette smoking to be associated with a marked increase in the risk for peripheral atherosclerosis. As well, Alonso & Garcia, (2011) carried out a study about Costs of Critical Limb Ischemia; they found relationship between smoking and severity of limb ischemia and revealed that smoking is the most important clinical predictor for critical limb ischemia.

Concerning Body mass index, the present study showed that more than two thirds of the studied sample was overweight; most of this group had severe peripheral ischemia, with a significant statistical relationship between BMI and severity of peripheral ischemia. Over weight and obesity from the researchers' point of view is an independent risk factor for many complications, of these; peripheral ischemia, especially when it is associated with restricted mobility and receiving such drugs as vasopressors. This finding is in agreement with that of Ciocan, et al, (2017) who studied demographic and comorbidity pattern of patients with limb ischemia and found that most involved patients overweight. However, Murata, et al.,(2015) conducted a study about the relationship of Body Mass Index and mortality in patients with Critical Limb Ischemia, and showed contradiction with the present study finding, they found that underweight patients had an extremely poor prognosis as compared to those with normal BMI and overweight/obese.

Therefore, from what has been introduced, critically ill patients receiving high alert medications experience great challenges which is peripheral ischemia. They had alteration in perfusion as a result of having cardiogenic and septic shock, in addition to other medical and demographic characteristics which from the researchers' point of view accelerated their worse progress. Therefore, the critical care nurse must be aware of preparation, concentration, dose calculation, and route of administrating high alert medications. The nurse must be aware that these drugs must be administered only via the intravenous route, infused preferably by a central catheter using an infusion pump or other device to control the flow rate, and not to be administered into the veins of the legs especially in elderly patients. The nurse should monitor patients' hemodynamic variables frequently until stabilized; of these are blood pressure, peripheral pulse, temperature, oxygen saturation and monitor ECG. In addition, caution is needed to avoid extravasation drugs such as norepinephrine and epinephrine during intravenous administration through frequent check the infusion site (John, Arifulla, Cheriathu & Sreedharan, 2012).

Moreover, accurate assessment and physical examination of patients receiving high alert medications for detection of early signs of altered peripheral perfusion is an important critical

care nursing consideration. It improves patients' prognosis and prevents serious complications that may lead to limb loss (Chung, Modrall, Ahn, Lavery & Valentine, 2015). As well, care of ischemic limbs requires perfusion assessment, pain assessment and control, edema control with leg elevation and avoiding massive compression wrapping or stockings, and utilizing aseptic techniques (Brem, et al, 2017).

CONCLUSION

Severe upper and lower peripheral/limb ischemia was a common associated vascular complication among critically ill patients receiving vasopressors in the present study. In addition to the effect of theses potent vasoactive drugs on patients' hemodynamic status, comorbidity diseases such as diabetes and hypertension, increased age, male gender, smoking, and overweight were among factors that significantly related to severity of ischemia. Thus, establishing multidisciplinary efforts is required for management of patients receiving high alert drugs.

RECOMMENDATIONS

1. Meticulous focused and comprehensive assessment is important nursing consideration for critically ill patients receiving vasopressors.
2. Establishment of standardized assessment tools that facilitate prediction and detection of peripheral ischemia among critically ill patients.
3. Availability of illustrated guidelines to facilitate continuity of care for patients receiving high alert medications.
4. Replication of the study on a larger probability sample selected from different geographic areas in Egypt.

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