Introduction

No one can contemplate the prospect of an operation without some nervousness or apprehension. Premedication is an important step before giving anesthesia to patient ***(Matot et al., 2000).***

A major goal of anesthesiologist is to attenuate the hemodynamic and autonomic responses to noxious stimuli, while preserving adequate circulatory function. The demand of patients is to face the operation with calm, confidence and without anxiety. For general anesthesia (GA), Laryngoscopy and endotracheal intubation are done frequently which is invariably associated with rise in heart rate (HR), arterial blood pressure (ABP), and occasional disturbance of cardiac rhythm. These hemodynamic responses arise as a form of sympathoadrenal reflex. This adrenergic stress response is extremely harmful in patients with cardiac disorders, old age, hypertensive patients, and neurological disturbances ***(Das et al., 2013).***

A number of drugs have been used for attenuation of the cardio-vascular response. The list includes topical lignocaine, intravenous (IV) lignocaine, IV Hydralazine, volatile anesthetic agents, narcotic analgesics, adrenergic blockers, and vasodilators like nitroglycerine and nifedipine, etc.

Midazolam, a benzodiazepine, is the most commonly used premedication because of its anxiolytic and hypnotic effect, a short elimination half-life and high clearance, better anterograde amnesia, and minor effect on hemodynamic and respiratory inhibition compared to other benzodiazepines ***(Almenrader et al., 2007).***

Clonidine has been utilized as a preoperative medication to provide sedation, analgesia, hemodynamic stability, control of salivation and antiemetic effects. It also possesses anesthetic, and analgesic sparing properties that reduce the dosages of other medications ***(Bergendahl et al., 2006).***

This study was conducted to compare the clinical efficacy of oral premedication with clonidine 200μg versus midazolam 15mg as regarding attenuation of hemodynamic response to intubation, sedation, analgesia and adverse effects in hypertensive patients undergoing general anesthesia for a variety of surgeries.

Pain is an unpleasant sensation that originates from ongoing and impending tissue damage. Acute pain accompanies almost all surgical procedures. Adequate pain relief provides a quick return to normal physiological function and prevents the development of chronic pain. Traditional analgesia in the post-operative period is based on opioids, non-steroidal anti-inflammatory drugs (NSAIDS) and regional techniques. Administration of high doses of opioids during the

post-operative period can result in higher incidence of complications such as respiratory depression, vomiting, constipation, pruritus, immune dysfunction and urinary retention. NSAIDS may lead to gastrointestinal bleeding, renal toxicity and thromboembolic complications. Regional analgesia techniques require additional intervention and have the potential risk of complications such as hypotension, bradycardia and toxicity of the administered drug. Hence, the search for an ideal drug continues. A drug, which has anxiolytic property without the adverse effects of traditional analgesics mentioned, may be an attractive choice for post-operative analgesia. Clonidine has anti-nociceptive properties without any of the previous complications ***(Prasad et al., 2014).***

Aim of the Work

The Primary outcome of the study was to compare the BP, HR changes during laryngoscopy and endotracheal intubation between oral clonidine and oral midazolam in hypertensive patients undergoing GA.

Secondary outcome was to compare the preoperative sedation status, postoperative analgesia and possible adverse effects of these two drugs.

Chapter 1

Pathogenesis of Essential Hypertension

The pathogenesis of essential hypertension is multifactorial and highly complex. the kidney is both the contributing and the target organ of the hypertensive processes, and the disease involves the interaction of multiple organ systems and numerous mechanisms of independent or interdependent pathways. Factors that play an important role in the pathogenesis of hypertension include genetics, activation of neurohormonal systems such as the sympathetic nervous system and renin-angiotensin-aldosterone system, obesity, and increased dietary salt intake ***(Oparil et al., 2003).***

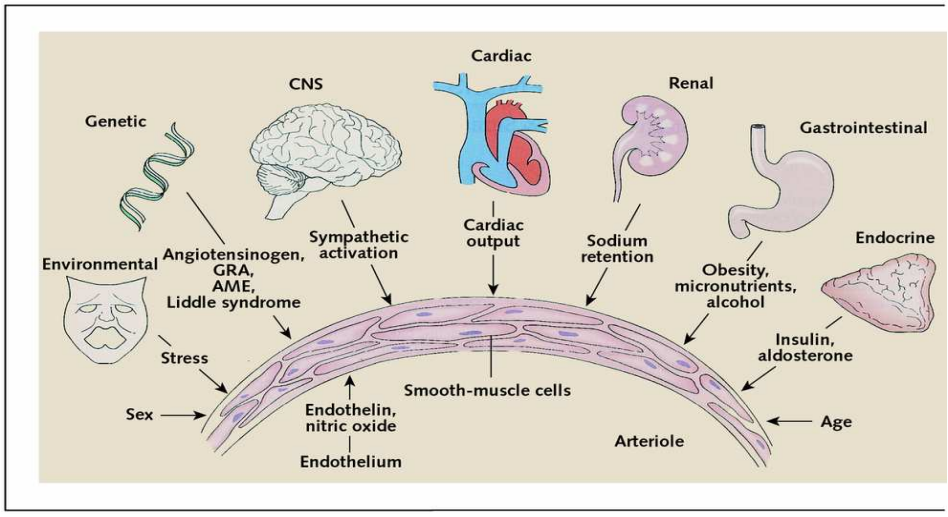

Figure (1): Factors contributing in essential hypertension ***(Oparil et al., 2003).***

Arterial hypertension is the condition of persistent elevation of systemic arterial blood pressure (ABP). ABP is the product of cardiac output and total peripheral vascular resistance. Multiple factors are involved in short-term and long-term regulation of ABP for adequate tissue perfusion; these include the following:

a- Cardiac output and circulatory blood volume.

b- Vascular caliber, elasticity, and reactivity.

c- Humoral mediators.

d- Neural stimulation ***(Bolívar, 2013).***

Over the course of its natural history, essential hypertension progresses from occasional to established hypertension. After a long, invariable, asymptomatic period, persistent hypertension develops into complicated hypertension, in which target organ damage to the aorta and small arteries, heart, kidneys, retina, and central nervous system is evident ***(Laurent et al., 2003).***

Hypertension is a chronic elevation of blood pressure that, in the long-term, causes end-organ damage and results in increased morbidity and mortality. It follows that patients with arterial hypertension may have an increase in cardiac output, an increase in systemic vascular resistance, or both. In the younger age group, the cardiac output is often elevated, while in older patients increased systemic vascular resistance and increased

stiffness of the vasculature play a dominant role. Vascular tone may be elevated because of increased α-adrenoceptor stimulation or increased release of peptides such as angiotensin or endothelins. The final pathway is an increase in cytosolic calcium in vascular smooth muscle causing vasoconstriction. Several growth factors, including angiotensin and endothelins, cause an increase in vascular smooth muscle mass termed vascular remodeling. Both an increase in systemic vascular resistance and an increase in vascular stiffness augment the load imposed on the left ventricle; this induces left ventricular hypertrophy and left ventricular diastolic dysfunction ***(Foëx, 2004).***

In youth, the pulse pressure generated by the left ventricle is relatively low and the waves reflected by the peripheral vasculature occur mainly after the end of systole, thus increasing pressure during the early part of diastole and improving coronary perfusion. With ageing, stiffening of the aorta and elastic arteries increases the pulse pressure. Reflected waves move from early diastole to late systole. This results in an increase in left ventricular afterload, and contributes to left ventricular hypertrophy. The widening of the pulse pressure with ageing is a strong predictor of coronary heart disease ***(Yusuf et al., 2000).***

The autonomic nervous system plays an important role in the control of blood pressure. In hypertensive patients, both increased release and enhanced peripheral sensitivity to norepinephrine can be found. In addition, there is increased

responsiveness to stressful stimuli. Another feature of arterial hypertension is a resetting of the baroreflexes and decreased baroreceptor sensitivity. The renin–angiotensin system is involved at least in some forms of hypertension (e.g. Renovascular hypertension) and is suppressed in the presence of primary hyperaldosteronism. Elderly or black patients tend to have low-renin hypertension. Others have high-renin hypertension and these are more likely to develop myocardial infarction and other cardiovascular complications ***(Cain and Khalil, 2002).***

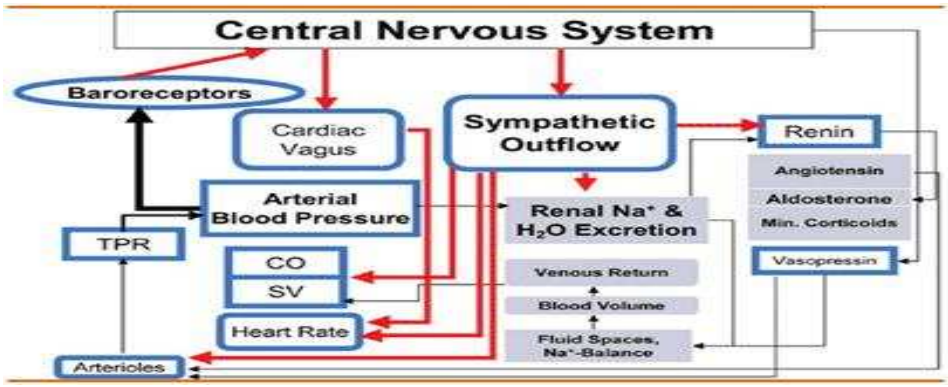

Figure (2): The role of RAAS and catechol amines in pathogenesis.***(Williams et al., 2004).***

In human essential hypertension, and experimental hypertension, volume regulation and the relationship between blood pressure and sodium excretion (pressure natriuresis) are abnormal. Considerable evidence indicates that resetting of pressure natriuresis plays a key role in causing hypertension. In patients with essential hypertension, resetting of pressure natriuresis is characterized either by a parallel shift to higher blood pressures and salt-insensitive hypertension, or by a

decreased slope of pressure natriuresis and salt-sensitive hypertension ***(Williams et al., 2004).***

The progression of essential hypertension begins with prehypertension in persons aged 10-30 years (by increased cardiac output); then advances to early hypertension in persons aged 20-40 years (in which increased peripheral resistance is prominent); then progresses to established hypertension in persons aged 30-50 years; and finally advances to complicated hypertension in persons aged 40-60 years ***(Bolívar, 2013).***

Stages of hypertension: *(National Committee VI Guideline, 2009)*

(Systolic and diastolic pressures given in mm Hg.)

Table (1): Stages of hypertension.

Stage	Systolic ABP	Diastolic ABP
Optimal	<120	<80
Normal	120–129	80–84
High-normal	130–139	85–89
HT stage 1	140–159	90–99
HT stage 2	160–179	100–109
HT stage 3	>180	>110

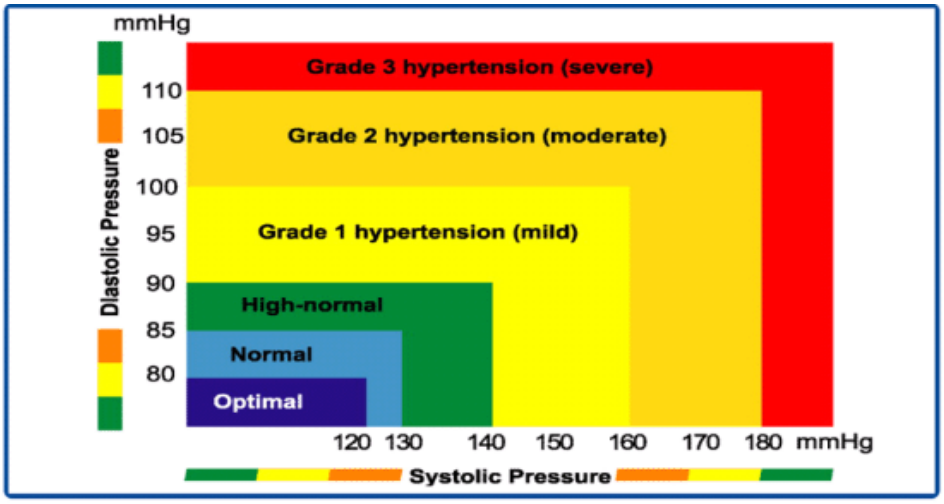

Figure (3): Stages of hypertension.*(National Committee VI Guideline, 2009)*

Chapter 2

Regulation of Blood Pressure

Factors Influencing ABP Regulation:

Regulation of normal Arterial blood pressure (ABP) is a complex process. Cardiac output is the product of stroke volume and heart rate. The factors affecting cardiac output include sodium intake, renal function, and mineralocorticoids. The inotropic effects occur via extracellular fluid volume augmentation and an increase in heart rate and contractility ***(Coruzzi et al., 2005).***

Peripheral vascular resistance is dependent upon the sympathetic nervous system (SNS), humoral factors, and local autoregulation. The vasculature is highly innervated by sympathetic fibers. The SNS produces its effects via the vasoconstrictor alpha effect or the vasodilator beta effect. Along the same line, the renal artery is highly innervated, with the sympathetic activation promoting sodium retention via increased renin secretion ***(Barbato et al., 2004).***

The role of renal nerves in ABP control and in the pathogenesis of hypertension has been made evident by the effect of renal denervation (RDN) in animal model experiments. The physiologic mechanisms that account for the heterogeneous decrease in arterial BP following RDN remain unclear and may indicate factors more than simply high renal sympathetic activity. Of all of the variables examined that

could influence BP outcomes, the extent of the RDN seems to be of great significance. Respectively, RDN might work if done properly and if used in the appropriate patient population ***(Robert et al., 2000).***

Similarly, the role of the arterial baroreflex system in moment-to-moment regulation of ABP is well known. Although electrical stimulation of baroreceptors can cause significant reduction in BP in humans with treatment-resistant hypertension, its importance in long-term ABP control remains controversial. These studies confirm the role of the SNS as a component in the pathogenesis of hypertension ***(Pao, 2014).***

The humoral actions on peripheral vascular resistance are a result of mediators, such as vasoconstrictors eg, endothelin [ET], angiotensin II [Ang II], catecholamines or vasodilators (eg, nitric oxide [NO], prostaglandins, kinins). In addition, blood viscosity, vascular wall shear conditions (rate and stress), and blood flow velocity (mean and pulsatile components) have potential relevance with regard to the regulation of BP in humans by vascular and endothelial function**.** Circulating blood volume is regulated by renal salt and water handling, a phenomenon that plays a particularly important role in salt-sensitive hypertension and in the setting of chronic kidney disease ***(Horacio et al., 2007).***

Autoregulation of ABP:

Autoregulatory mechanisms maintain the blood flow of most tissues over a wide range of ABP according to their

specific needs. Autoregulation of ABP occurs by way of intravascular volume contraction and expansion regulated by the kidney, as well as via transfer of transcapillary fluid. Through the mechanism of pressure natriuresis, salt and water balance are achieved at heightened systemic pressure Interactions between cardiac output and peripheral vascular resistance are autoregulated to maintain a set ABP in an individual. For example, constriction of the arterioles elevates arterial pressure by increasing total peripheral vascular resistance, whereas venular constriction leads to redistribution of the peripheral intravascular volume to the central circulation, thereby increasing preload and cardiac output ***(Pao, 2014).***

Vasoreactivity and the role of the vascular endothelium

The vasoreactivity of the vascular bed, an important phenomenon mediating changes of hypertension, is influenced by the activity of vasoactive factors, reactivity of the smooth muscle cells, and structural changes in the vessel wall and vessel caliber, expressed by a lumen-to-wall ratio.

The vascular endothelium is considered to be a vital organ, in which synthesis of various vasodilating and constricting mediators occurs. The interaction of autocrine and paracrine factors takes place in the vascular endothelium, leading to growth and remodeling of the vessel wall and to the hemodynamic regulation of ABP ***(Heine et al., 2003).***

Chapter 3

Etiology of Essential Hypertension

Essential hypertension (also called idiopathic hypertension) may be attributed to multiple factors, including genetic predisposition, excess dietary salt intake, and adrenergic tone, that may interact to produce hypertension. Essential hypertension accounts for 90% of human hypertension and can evolve into secondary hypertension, as renal function decreases. Thus, the distinction between primary and secondary forms of hypertension is not always clear in patients who have had uncontrolled hypertension for many years ***(Hall et al., 2006).***

Long-term regulation of daily blood pressure (BP) is closely linked with salt and water homeostasis. Increased BP raises renal sodium and water excretion, often called renal-pressure natriuresis or diuresis. Increased salt intake in persons who have normal kidney and neurohormonal functions has an insignificant effect on BP changes. These individuals are called "salt resistant." In contrast, in "salt-sensitive" individuals with impaired kidney function, because of abnormal neurohormonal control or intrinsic kidney abnormalities, increased BP and subsequent pressure natriuresis or diuresis provide another means of maintaining salt and water balance. That is, sodium balance is maintained at a higher BP in patients with primary hypertension, indicating that pressure natriuresis has been reset ***(Heine et al., 2003).***

There are two types of genetic causes of hypertension:

Rare familial monogenic hypertensive disorders and classic quantitative trait form. The rare monogenic disorders, which account only for a very small percentage of hypertension in humans, increase renal sodium reabsorption and induce low renin hypertension due to volume expansion. They compromise eight monogenic hypertensive syndromes that are subdivided based on aldosterone level and the presence of special features.

Syndromes with elevated aldosterone level include the following:

- Glucocorticoid remediable aldosteronism (GRA) or familial hyperaldosteronism type I (FH1). The underlying gene is CYP11B2.
- Gordon hyperkalemia-hypertension syndrome or pseudohypoaldosteronism type II (PHA2). The genes involved are WNK kinases 1 and 4 (WNK1, WNK4) or KLHL3 and CUL3.
- Familial hyperaldosteronism type III (FH3). The mutated gene is KCNJ5.

Syndromes with low aldosterone level include the following:

- Liddle syndrome or pseudoaldosteronism. The mutated genes are SCNN1B and SCNN1G.
- Syndrome of apparent mineralocorticoid excess. HSD11B2 is the involved gene.