Attenuation of Cardiovascular and Hormonal Responses during and after Laparoscopic Cholecystectomy: A Comparative Study between Dexmedetomidine and Magnesium Sulphate

Thesis

Submitted for Partial Fulfillment of M.D.
in Anesthesia and Intensive Care

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2015

صدق الله العظيم

سورة النساء ۞ الآية { ١١٣ }

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotrophic hormone
CNS	Central nervous system
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
HPA	Hypothalamic-pituitary-adrenal axis
ICP	Intracranial pressure
ICU	Intensive care unit
MgSO4	Magnesium sulfate
NMDA	N-methyl-D-aspartate
TSH	Thyroidstimulating hormone
α_2-AR	α2-adrenergic receptor
PP	Pneumoperitoneum
LH	Leuteinizing hormone
$MgCl_2$	Magnesium chloride
MRI	Magnetic resonant imaging
PACU	Post anesthesia care unit
MAP	Mean arterial pressure
HR	Heart rate
VAS	Visual analogue scale
LC	Laparoscopic cholecystectomy
DOA	Depth of anesthesia

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INTRODUCTION

Surgical trauma causes reaction and damage in the patient in proportion to the extent of the operation. It is associated with complex stress response characterized by neuro-humoral, immunological and metabolic alterations. Activation of sympathetic nervous system and increased release of catabolic and immuno-suppressive pituitary hormones can be attributable to surgical stress response. In clinical practice, these activations cause changes in heart rate and blood pressure and alterations in biochemical measurements like noradrenaline, adrenaline, dopamine and cortisol levels. The type of surgical procedure, either open or laparoscopic cholecystectomy, reflects the severity of traumatic stress imposed to the patient ***(Nishiyama et al., 2005).***

Laryngoscopic manipulation and endotracheal intubation increase the release of catecholamine by stimulating the sympathetic nervous system and this results in the elevation of blood pressure and heart rate, and occurrence of arrhythmias. This response could lead to severe situations like myocardial ischemia for patients who have risk factors of hypertension and ischemic heart disease. For these reasons, local anesthetics, beta blockers, and opioids have been used in order to prevent changes in the

cardiovascular system when endotracheal intubation is performed ***(Lee et al., 2012).***

Pneumoperitoneum with carbon dioxide insufflation for laparoscopic surgery induces cardiovascular response characterized by abrupt elevation of arterial pressure and systemic vascular resistance. These vasopressor responses are likely to be due to increased release of chatecholamines, vasopressin, or both ***(Mann et al., 1999).***

Magnesium sulphate blocks the release of catecholamines from adrenergic nerve terminals and also from the adrenal gland. Intravenous magnesium sulphate inhibits catecholamine release associated with tracheal intubation. Moreover, magnesium produces vasodilatation through acting directly on blood vessels ***(Jee et al., 2009).*** High-dose magnesium attenuates vasopressin-stimulated vasoconstriction and normalizes sensitivity to vasopressin ***(Laurant et al., 1997).***

Dexmedetomidine is a selective alpha 2- adrenergic agonist with evidence of an increased ratio of alpha 2 to alpha 1 activity of 1620:1. Alpha 2-adrenergic agonists produce analgesia and sedation which is likely to be multi-factorial. Dexmedetomidine also lacks respiratory depression that may make it a useful and safe adjunct in many diverse clinical applications ***(Thomas and Halaszynski, 2012).***

AIM OF THE WORK

The aim of this work was to compare the effect of intravenous dexmedetomidine and magnesium sulphate on the hemodynamic changes and hormonal responses to tracheal intubation and pneumoperitoneum during laparoscopic cholecystectomy under general anesthesia.

PERIOPERATIVE STRESS RESPONSE

Stress is a term applied in the fields of physiology and neuroendocrinology to refer to those forces or factors that cause disequilibrium to an organism and; therefore, threaten homeostasis. The stressors can be defined physical injury, mechanical disruption, chemical changes, or emotional factors, and the body's response to these factors can be carefully quantitated.

In mammals, complex sensory systems evolve that result in reflex nervous system responses to the stressor and also alert the central nervous system (CNS) to the disturbance. Neurons of the paraventricular nucleus of the hypothalamus elaborate corticotropin-releasing hormone and activate the hypothalamic-pituitary-adrenal axis (HPA). Other areas of the brain stem signal the peripheral autonomic nervous system. These two systems elicit an integrated response, referred to collectively as the "stress response, " which primarily controls bodily functions such as arousal, cardiovascular tone, respiration, and intermediate metabolism. Activation of this system also influences many other functions of the CNS, such as feeding and sexual behavior, which are suppressed, and cognition and emotion, which are activated. In

addition, this system alters normal gastrointestinal activity and depresses immune/inflammatory reactions ***(Wilmor, 2002).***

The system response to surgical trauma includes activation of the sympathetic nervous system, the endocrine "stress response", and immunological and hematological changes. Various kinds of stress cause an increase in the secretion of adrenocrticotrophic hormone (ACTH) from the adenohypophysis, and; within a few minutes, an increase in secretion of cortisol from the adrenal cortex occurs. Cortisol is considered to be a significant hormone in stress. Many different, non-specific stimuli can cause a noticeable increase in secretion of cortisol from the adrenal cortex (e.g., trauma, surgery, infection, strong heat or cold, and almost any debilitating disease). Generally, the level and duration of increase in intra-and postoperative concentrations of cortisol are in proportion to the degree of surgical trauma ***(Antanaskovic et al., 2012).***

The etiology of hyperglycemia in stress is multi-factorial, but is thought primarily to be the result of activation of the sympathoadrenal system, with contributions from the hypothalamus and adenohypophysis. The stress response triggers an increase in levels of plasma catecholamines and glucocorticoids, which in turn lead to hyperglycemia. Cortisol also has a huge impact on the glucose metabolism in stress, because by

increasing glycogenolysis and gluconeogenesis it can lead to hyperglycemia ***(Snezana et al., 2014).***

Clinical implications of stress response involve hypertension, tachycardia, arrhythmia, myocardial ischemia, protein catabolism, suppression of the immune response, and loss of the excretory renal function with retention of electrolytes and water. Stress response is a significant risk factor for an unsatisfactory outcome in patients with cardiovascular disease, in patients with known endocrine, metabolic and immune disorders, as well as in patients with infection and immunosuppression. Thus, the reduction and modulation of stress response during the operation can significantly reduce the incidence of postoperative complications and morbidity ***(Bochicchio and Scalea, 2008).***

The endocrine response to surgery

The stress response to surgery is characterized by increased secretion of pituitary hormones and activation of the sympathetic nervous system. The changes in pituitary secretion have secondary effects on hormone secretion from target organs. For example, release of corticotrophin from the pituitary stimulates cortisol secretion from the adrenal cortex. Arginine vasopressin is secreted from the posterior pituitary and has effects on the kidney. In the pancreas, glucagon is released and insulin secretion may be

diminished. The overall metabolic effect of the hormonal changes is increased catabolism which mobilizes substrates to provide energy sources, and a mechanism to retain salt and water and maintain fluid volume and cardiovascular homeostasis.

Sympathoadrenal response

Hypothalamic activation of the sympathetic autonomic nervous system results in increased secretion of catecholamines from the adrenal medulla and release of norepinephrine from presynaptic nerve terminals. Norepinephrine is primarily a neurotransmitter, but there is some spillover of norepinephrine released from nerve terminals into the circulation. The increased sympathetic activity results in the well recognized cardiovascular effects of tachycardia and hypertension. In addition, the function of certain visceral organs, including the liver, pancreas and kidney, is modified directly by efferent sympathetic stimulation and/or circulating catecholamines ***(Desborough, 2002).***

Stress response induces elevations in the metabolic rate in an attempt to restore homeostasis. Although initially beneficial, the exaggerated and prolonged inflammatory, metabolic, and catabolic responses induce clinical complications, delay recovery, and increase mortality. Significant basal metabolic rate (BMR) elevations occur reaching 30% or more of total body surface area.

Inflammatory, hormonal, and stress signaling mechanisms drive the hypermetabolic response including elevations of circulating catecholamines, glucocorticoids, and glucagon, with subsequent increases in gluconeogenesis, glycogenolysis, and protein catabolism. Insulin resistance and peripheral lipolysis develop as well ***(Finnerty et al., 2013)***.

The hypothalamic–pituitary–adrenal axis

Anterior pituitary

Anterior pituitary hormone secretion is stimulated by hypothalamic releasing factors. The pituitary synthesizes corticotrophin or ACTH as part of a larger precursor molecule, pro-opiomelanocortin. The precursor is metabolized within the pituitary into ACTH, β-endorphin and an N-terminal precursor. Growth hormone and prolactin are also secreted in increased amounts from the pituitary in response to a surgical stimulus. Concentrations of the other anterior pituitary hormones, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) do not change markedly during surgery ***(Lyons and Meeran, 1997).***