Faculty of Medicine
Department of Anesthesia
Intensive Care & Pain

Evaluation of the Safety and Efficacy of Dexmedetomidine as an Anesthetic Adjuvant in Coronary Artery Bypass Grafting Surgeries

Thesis

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By

Mohammed Khaled Abdelhameed Ahmed Shaker
M.B., B.Ch. M.Sc., Ain Shams University

Supervised by

Prof.Dr. Omar Mohamed Taha El-Safty
Professor of Anesthesiology, Intensive Care and Pain Management
Faculty of Medicine, Ain Shams University

Prof. Dr. Abeer Mohamed Abdel-Aziz El-Deek
Assistant Professor of Anesthesiology, Intensive Care and Pain Management
Faculty of Medicine, Ain Shams University

Dr. Dalia Ahmed Ibrahim Mohamed
Lecturer of Anesthesiology, Intensive Care and Pain Management
Faculty of Medicine, Ain Shams University

Dr. Hany Magdy Fahim Hanna
Lecturer of Anesthesiology, Intensive Care and Pain Management
Faculty of Medicine, Ain Shams University

Faculty of Medicine
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بسم الله الرحمن الرحيم

﴿وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللهِ عَلَيْكَ عَظِيمًا﴾

صدق الله العظيم

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Mohammed Khaled Shaker

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List of Abbreviations

Abb.	Full term
ACTH	*Adreno-corticotrophic hormone*
AF	*Atrial fibrillations*
AMP	*Adenosine mono phosphate*
ARF	*Acute renal failure*
CABG	*Coronary artery bypass grafting*
CAD	*coronary artery disease*
C-AMP	*Cyclic-adenosine mono phosphate*
CBC	*Complete blood picture*
CNS	*Central nervous system*
CPB	*Cardio-pulmonary bypass*
CRP	*C-reactive protein*
DBP	*Diastolic blood pressure*
DC	*Direct current*
ECG	*Electrocardiograph*
FDA	*Food and drug administration*
GABA	*Gamma amino butyric acid*
IABP	*Intra aortic balloon pump*
ICU	*Intensive care unit*
IL	*Interleukin*
INR	*International normalized ratio*
IU	*international unit*
IV	*Intravenous*
KFT	*Kidney functions test*
LFT	*Liver functions test*
MACE	*Major adverse cardio-cerebral events*
MBP	*mean blood pressure*
MI	*Myocardial infarction*
OR	*Operating room*

List of Abbreviations Cont...

Abb.	Full term

PT..... Partial thrombin time
PTT..... partial thromboplastin time
RBS..... Random blood sugar
SBP..... Systolic blood pressure
STS..... Society of thoracic surgeons
SVR..... Systemic vascular resistance
SVT..... Supra ventricular tachycardia
TMN..... Tubero-mamillary nucleus
TNF..... Tumor necrosis factor
VF ..... Ventricular fibrillation
VLPO ..... Ventrolateral pre-optic nucleus

INTRODUCTION

Coronary artery disease (CAD) continues to be a leading cause of morbidity and mortality worldwide. Although epidemiologic evidences suggest that there has been a reduction in death attributable to ischemic heart disease in recent years, it still has a considerably high morbidity and mortality rates ***(Lamy et al., 2012)***.

Coronary artery bypass grafting surgery (CABG) still is a main treatment procedure up till now, unfortunately comes with a considerable high rates of complications. The 30-day mortality is about 1.2% in the on-pump coronary artery bypass grafting (CABG) surgery, and in elderly patients (>65 years) mortality is 8.1% at 1 year ***(Shahian et al., 2012).***

There are approximately 7 million invasive cardiovascular procedures are performed worldwide each year. The major complication rates for coronary artery bypass grafting (CABG) procedures are as high as 30.1% in Society of Thoracic Surgeons (STS) reports. Postoperative delirium, infection, acute renal failure (ARF), and major adverse cardio-cerebral events (MACE) which include permanent or transient stroke, coma, myocardial infarction (MI), heart block and cardiac arrest represent major postoperative complications with more than 50% of all perioperative complications are related to adverse cardiovascular events. These complications are translated into increased mortality and prolonged hospital stays with estimated costs

exceeding $20 billion annually. The etiologies of these adverse events are multifactorial, but one major contributing factor is the surgical stress response ***(Fuhai et al., 2016).***

Alpha-2 receptors are a subgroup of noradrenergic receptors that mediate the function of the sympathetic nervous system. The alpha-2 receptor is probably the body's most important presynaptic receptor; its activation results in reduction in nor- epinephrine release, which can be used therapeutically to induce sympatholysis and control surgical stress response ***(Venn et al., 2001).***

Dexmedetomidine is an alpha 2-agonist approved in 1999 by FDA for sedation in adult patients in the ICU setting. The use of dexmedetomidine in the ICU could facilitate weaning from mechanical ventilation and improve quality of sedation and pain control for postoperative period following cardiac surgery which has been described in multiple studies. Clinical trials of its usage in non-cardiac surgeries demonstrate how the use of dexmedetomidine reduces requirements of intravenous and inhalational anesthetic agents, provides intraoperative hemodynamic stability and reduces the requirements of postoperative opioid analgesics. However, there is limited information about the intraoperative use of dexmedetomidine in cardiac surgery as an adjuvant of the anesthetic technique ***(Venn et al., 2001).***

Aim of the Work

The aim of this work is to evaluate the potential benefits and risks of intraoperative usage of dexmedetomidine as an adjuvant to anaesthesia in coronary artery bypass grafting surgeries.

Chapter 1

STRESS RESPONSE

The stress response to surgery is a major neuroendocrine and cytokine response of the body to surgical trauma, characterized by increases in catecholamine and steroid hormones release, with predictable metabolic consequences. This stress response has been considered as the homeostatic defense mechanism, important for the body for adaptation and developing resistance to the noxious insults as surgical procedures.

Such exaggerated physiological changes in patients with coexisting diseases is always life threatening. If the stress response is prolonged, the continuous hypermetabolic state may result in exhaustion of essential components of the body causing loss of weight, fatigue, decreased resistance, delayed ambulation and increased morbidity and mortality especially myocardial oxygen supply demand imbalance and myocardial ischemia ***(Velickovic et al., 2002).***

Although there are many contributing factors to the adverse events accompany coronary artery bypass grafting surgery (CABG), surgical stress response is one of the most important factors in the pathogenesis of these complications, and attenuation of its wide range of endocrinological, immunological and haematological effects deliver safe on-pump cardiac surgery ***(Brown et al., 2008)***.

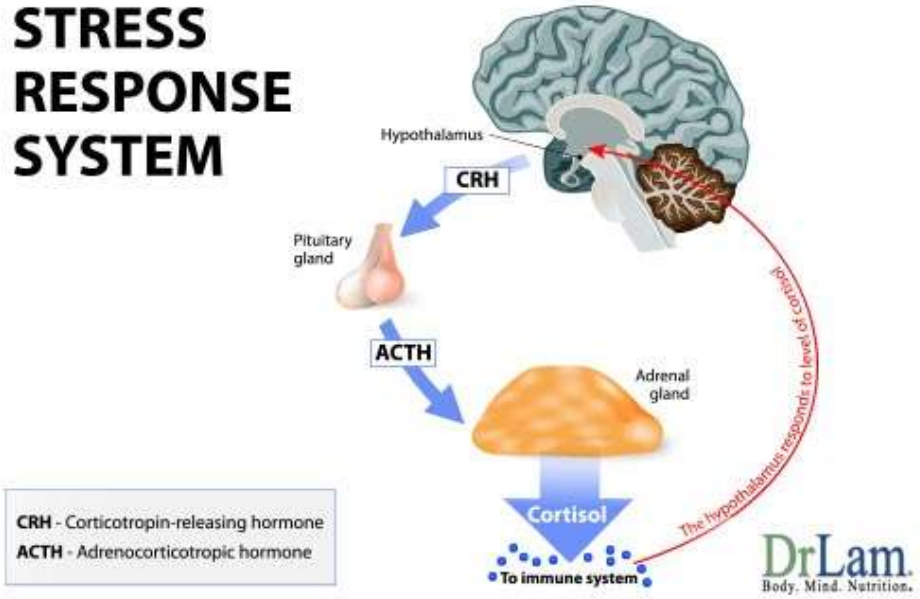

Figure (1): Stress response system (www.drlam.com).

Activation of the stress response

The endocrine response is activated by afferent neuronal impulses from the site of injury. These travel along sensory nerve roots through the dorsal root of the spinal cord, up the spinal cord to the medulla to activate the hypothalamus ***(Sheeran and Hall, 2007)***.

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 ***(Talke et al., 2010)***.

The humoral and 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 (figure 1). 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 ***(Desborough and Hall, 2003)***.

Cortisol is a one of the most important indicators of severity of the stress response the patient undergo. Cortisol secretion from the adrenal cortex increases rapidly following the start of surgery, as a result of stimulation by ACTH. From baseline values of around 400 nmol/litre^{-1}, cortisol