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Effect of Preoperative Pregabalin on Stress Response during Laryngoscopy and Intubation and on Postoperative Analgesia in Normotensive Normoglycemic Patients Undergoing Abdominal Hysterectomy

Thesis

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Ihab Ahmed Gadelrab

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List of Abbreviations

Abb.	Full term
ACTH	Adrenocorticotrophic hormone
AMPA	2-amino-3-hydroxy5-methyl-4-isoxazole-propionic acid
Ca^{2+}	Calcium
CBS	Capillary blood sample
CPSP	Chronic postsurgical pain
CRH	Corticotropin releasing hormone
DBP	Diastolic blood pressure
DPN	Diabetic peripheral neuropathy
FDA	Food and drug administration
GABA	Gamma-amino butyric acid
GABAA	Gamma-amino butyric acid A subunit
GABAB	Gamma-amino butyric acid B subunit
HPA	Hypothalamus-pituitary-adrenocortical
HR	Heart rate
KATP channels	Potassium Adenosine triphosphate channels
MBP	Mean blood pressure
NMDA	N-methyl-D-aspartate
NS neurons	Nociceptive specific neurons
PACU	Postanesthetic care unit
PHN	Postherpitic neuralgia
SBP	Systolic blood pressure
SD	Standard deviation
SPSS	Statistical Program for Social Science
VAS	Visual analogue scale
VDCCs	Voltage-dependent calcium channels
WDR neurons	Wide-dynamic range neurons

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INTRODUCTION

Endotracheal intubation is a main part of the daily work of anesthesiologists. Laryngoscopy and endotracheal intubation induce marked sympathetic hemodynamic effect resulting in cardiac response which may be fatal in some patients with cardiac problems ***(Salony et al., 2016).*** The appropriate premedications (anxiolytics or adrenergic blocking drugs), smooth induction of anesthesia, laryngoscopy and intubation by an expert anesthesiologist are methods to attenuate the pressor response of laryngoscopy ***(Shobhana and Purvi, 2011).***

Hyperglycemia is a state of elevated levels of blood glucose which could be detrimental to surgical patients. During operation, there are a lot of factors which could lead to stress-induced hyperglycemia, and one of them is noted during orotracheal intubation. Hyperglycemia may predispose the patients to both intraoperative and postoperative complications such as wound infection and delayed wound healing ***(Duggan et al., 2017).***

Oral pregabalin premedication is effective for attenuation of hemodynamic pressor response of airway instrumentation in a dose-related fashion. There is no affection of perioerative hemodynamic stability and no prolongation of recovery time ***(Rastogi et al. 2012).***

Postoperative pain in the form of hyperalgesia caused by surgical trauma can lead to chronic postoperative pain ***(Pogatzki et al., 2017)***. Preemptive analgesia is a concept in managing postoperative pain. Preemptive analgesia prevents sensitization of peripheral and central pain pathways caused by tissue damage ***(Kim et al., 2014).***

Pregabalin is an analogue of GABA, but it is not active on GABA receptors. Its action is to decrease neurotransmitters in the central nervous system such as glutamate, norepinephrine and substance P. That's why it has analgesic, anticonvulsant and anxiolytic actions and hence its favorable effect on postoperative pain ***(Snehalatha et al., 2015).***

Nerve Supply of the Airway

The sensory supply to the upper airway is derived from cranial nerves (**Figure 1)**. The mucous membrane of the nose is innervated by the ophthalmic division (V_1) of the trigeminal nerve anteriorly (anterior ethmoidal nerve) and by the maxillary division (V_2) posteriorly (sphenopalatine nerves). The palatine nerves provide sensory fibers from the trigeminal nerve (V) to the superior and inferior surfaces of the hard and soft palate.

The olfactory nerve (cranial nerve I) innervates the nasal mucosa to provide the sense of smell.

The lingual nerve [a branch of the mandibular division (V_3) of the trigeminal nerve] and the glossopharyngeal nerve (the ninth cranial nerve) provide general sensation to the anterior two thirds and posterior one third of the tongue respectively. Branches of the facial nerve (VII) and glossopharyngeal nerve provide the sensation of taste to those areas respectively.

The glossopharyngeal nerve also innervates the roof of the pharynx, the tonsils and the undersurface of the soft palate ***(Morgan and Mikhail, 2013).***

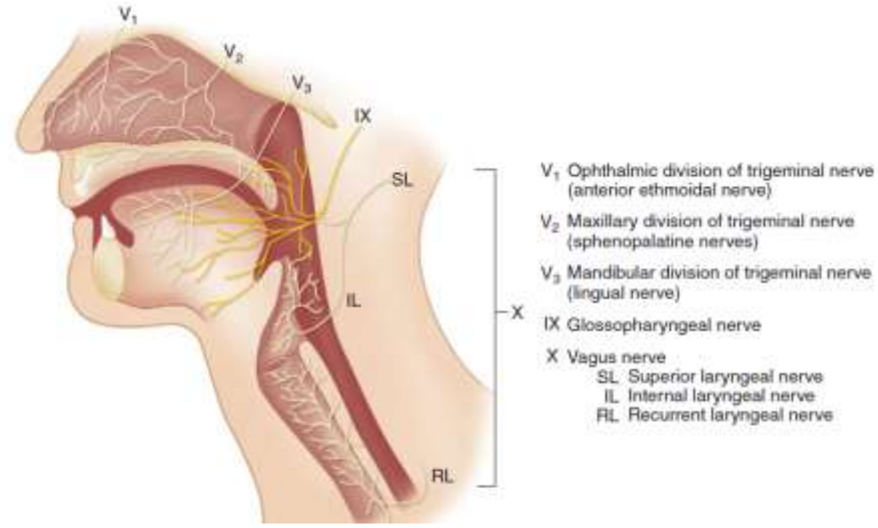

Figure (1): Nerve Supply of the Airway ***(Morgan and Mikhail, 2013).***

Innervation of the larynx:

Superior laryngeal nerve: It provides sensory supply to glottis and supraglottis. It provides motor fibers to the cricothyroid muscle which tenses the vocal cords.

Recurrent laryngeal nerve: It provides sensation to subglottis and motor fibers to all intrinsic muscles of larynx except the cricothyroid muscle ***(Morgan and Mikhail, 2013).***

Effect of mechanical stimulation of the airway:

***Hemodynamic response and the receptor location*:**

Mechanical stimulation of the upper respiratory tract; mainly the nose, the epipharynx, and the tracheobronchial tree, induces reflex cardiovascular responses associated with enhanced neuronal activity in cervical sympathetic efferent fibers ***(Kamlesh et al., 2016).***

The pressor response to the laryngoscopy and tracheal intubation is known to be a sympathetic response provoked by stimulation of the epipharynx (lies between the nasal cavity and oropharynx) and larynx. The largest reflex increase in blood pressure is evoked from the epipharyngeal region and the smallest from tracheobronchial tree ***(Kamlesh et al., 2016).***

Cardiovascular response to intubation is initiated by glossopharyngeal nerve (stimulus superior to anterior surface of epiglottis) and by vagus nerve (stimulus below posterior surface of epiglottis down into the lower airway). Hemodynamic response to laryngoscopy and intubation results in diffuse autonomic response with a widespread release of norepinephrine from adrenergic nerve terminals and secretion of epinephrine from adrenal medulla along with activation of the renin angiotensin system ***(Roopa et al., 2016).***

Physiological Aspects of Stress Response

Patients about to undergo anesthesia for surgery are almost inevitably anxious. Surgical procedures also induce complex stress responses, manifested by metabolic, neurohumoral, and immunological changes ***(Gupta et al., 2013).***

Stress response can be defined as a group of physiological and biochemical changes generated by the body in order to overcome a stressful condition which is called the “stressor”. Although stress response is a necessary mechanism for survival, severe stress disrupts normal structure and function of different organs ***(Al Kadhi, 2013).***

The physiologic response to stress consists of a rapid component and a slower one, acting in a coordinated manner to reestablish homeostasis. The rapid response is the activation of the sympathetic nervous system, which increases the levels of circulating norepinephrine and epinephrine and elevates the levels of norepinephrine in the brain. This is referred to as the “sympathetic-adrenomedullary system”. The slower, longer-lasting response is activation of the hypothalamic pituitary adrenal (HPA) axis that begins with the release of corticotrophin-releasing hormone (CRH) into the circulation from the paraventricular nucleus of the hypothalamus, which then stimulates the pituitary to release adreno-cortico-trophic hormone (ACTH) into the blood stream. The released ACTH accelerates the discharge of glucocorticoids from the adrenal cortex. The type-2 glucocorticoid receptors bind glucocorticoids at tenfold lower affinity than type-1 receptors. At the circulating low-basal glucocorticoid levels, type-1 receptors are already activated to a large extent. However, when the circulating glucocorticoid levels are elevated after stressful events, type-2 receptors are also activated. Glucocorticoid receptors are abundant throughout the brain. However, both receptor types are highly expressed in the hippocampus making it a target for stress hormone actions ***(Ulrich-Lai and Herman, 2009).***

These nuclear receptors can act as transcription factors by binding to the DNA, thus regulating gene expression. In addition, glucocorticoids mobilize peripheral energy stores, diminish the immune response, and mediate the negative feedback control of the HPA axis. Both the HPA axis and sympathetic-adreno-medullary system work in concert to coordinate adaptive responses to stressors. Regulation of the HPA axis occurs through negative feedback mechanisms in which high levels of glucocorticoids suppress the release of CRH ***(Al Kadhi, 2013).***

Excitation of the hypothalamus during stress results in the secretion of adreno-corticotrophic hormone (ACTH) from the pituitary gland which in turn, initiates increased secretion of cortisol from suprarenal glands with sudden increase in cortisol level. The metabolic effects of cortisol are directed to overcome the stressful state. Cortisol has widespread effects on the metabolism and utilization of glucose, amino acids and fatty acids in hepatic and extra-hepatic tissues. Cortisol causes rapid mobilization of amino acids and fat from their cellular stores, making them immediately available both for energy and synthesis of other compounds including glucose needed by different tissues ***(Stephens and Wand, 2012).***

The cortisol level in saliva is closely correlated with its level in blood and changes under stress. The sympathetic-adrenomedullary system secretes catecholamines: norepinephrine and epinephrine, but their detection in patients' blood is very complicated, as this calls for instant blood test and immediate freezing of the sample. Catecholamines are also excreted through saliva, but their level in saliva is not correlated with the level in blood. Reports have found differences between patient groups in hemodynamic indices, but not in the catecholamine level in blood serum ***(Nataïja et al., 2008).***

It has been suggested that increased circulating concentrations of catecholamines, glucagon, and cortisol can evoke the changes in carbohydrate metabolism, occurring immediately after trauma. The characteristic metabolic effect of cortisol is to decrease the rate at which insulin activates the glucose uptake system; hence, surgical stress leads to greater