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Attenuating Stress Response to Laryngoscopy and Intubation using Nebulized Ketamine and Magnesium Sulphate

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Abstract: Background: Globally, approximately 310 million surgeries are performed yearly, with many patients requiring endotracheal intubation to successfully conduct these procedures. Endotracheal intubation is a crucial aspect of modern anesthesia, as it provides several benefits, including maintaining the patency of the airway, preventing pulmonary aspiration, providing positive pressure ventilation, controlling the delivery of oxygen and eliminating carbon dioxide. However, stimulation of the upper respiratory tract during tracheal intubation under general anesthesia can lead to activation of the sympathoadrenal system, resulting in increased serum catecholamines. This can be a concern for patients who are at risk of developing hypertension or tachycardia. Therefore, it is important to carefully monitor the patient's vital signs and adjust the anesthesia plan as needed to minimize the risk of adverse effects. Ketamine has been used successfully to treat acute pain in intranasal form. Nebulized ketamine as an analgesic bypassing first pass metabolism and without the need for intravenous access, used to decrease the need for rescue analgesia during PACU care. Delivery of ketamine by inhalation is safe, accessible, and simple method. Advantages of this route include the possibility of ketamine administration outside the hospital setting in cases if no I.V. access line is required. Magnesium sulfate is used in anesthesia and sedation most frequently and in obstetrics. The high frequency of using magnesium attention being paid to this drug, as well as the introduction of multimodal analgesia and anesthesia techniques. Magnesium sulfate nebulization has a significant effect to attenuate the stress response to Endotracheal intubation in the form of attenuating increase of Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Heart Rate (HR), and Blood Glucose level.

Keywords: *Stress Response, Laryngoscopy,Intubation, Nebulized Ketamine, Magnesium Sulphate*

Introduction

Globally, approximately 310 million surgeries are performed yearly, with many patients requiring endotracheal intubation to successfully conduct these procedures [1].

Endotracheal intubation is a crucial aspect of modern anesthesia, as it provides several benefits, including maintaining the patency of the airway, preventing pulmonary aspiration, providing positive pressure ventilation, controlling the delivery of oxygen and eliminating carbon dioxide. However, stimulation of the upper respiratory tract during tracheal intubation under general anesthesia can lead to activation of the

sympathoadrenal system, resulting in increased serum catecholamines. This can be a concern for patients who are at risk of developing hypertension or tachycardia. Therefore, it is important to carefully monitor the patient's vital signs and adjust the anesthesia plan as needed to minimize the risk of adverse effects [2,3].

The responses to laryngoscopy and endotracheal intubation are believed to be mediated by somatovisceral reflexes, which originate from proprio-receptors located in the base of the tongue, epiglottis, hypopharynx, peritracheal area, and vocal cords. These reflexes are thought to be transmitted via the spinal cord and sympathetic nervous system. The efferent sympathetic outflow to the heart originates from the spinal cord between T1 and T4, while the outflow to the adrenal medulla originates from spinal cord between T3 and L3 [4].

The body's response to external stimuli, ranging from minor to severe, is a complex interplay of physiological reflexes which occur throughout the body. The response will be in the form of endocrinal, metabolic and biochemical reactions throughout the body. The magnitude of response is highly dependent on the severity, intensity and duration of stimulus. For triggering such reflex response, some substances between the hypothalamic pituitary axis, the classical neuro-endocrinal hormone system and autonomic nervous system is brought to this action and is called “stress response” [5].

The stress changes are well tolerated by normal healthy patients (ASA grade I). The changes return to normal in due course of time. In patients with hypertension, coronary artery disease, myocardial infarction, valvular heart disease, aortic aneurysm, cerebral aneurysm or intracranial hypertension, diabetes mellitus, liver diseases, renal insufficiency, geriatric age group, (ASA grade III, IV, and V), these changes are life threatening [6].

Stress response if prolonged, the continuous hypermetabolic state may result in exhaustion of essential components of the body e.g. glucose, fat, protein, minerals, causing loss of weight, fatigue, decreased resistance, delayed ambulation and increased morbidity and mortality [7].

The net effect of stress response “The Neuroendocrinal outflow” [8]:

Cardiovascular changes: - Rise in-cardiac output, heart rate, blood pressure, increased myocardial contractility, increase oxygen demand.

Blood volume distribution: - Peripheral and splanchnic vasoconstriction coronary and cerebral vasodilatation.

Respiratory Changes:- Increased respiratory rate.

Fluid and electrolyte changes:- Sodium and water retention.

Coagulation:- Hypercoagubility and fibrinolysis

Immunosuppression:- Wound Infections

Metabolic Changes:- Substrate mobilization - hyperglycemia**.**

Urinary changes:- Reduced urinary output.

Laryngoscopy alone generates essentially the same pressor response as done by laryngoscopy followed by intubation. It starts within 5 seconds and reaches a peak in 1–2 min and returns to baseline within 10 minutes [9].

Direct laryngoscopy involves stretching the oropharyngeal tissues while the patient is under general anesthesia in an attempt to straighten the angle between the mouth and the glottis opening; however, this causes pain and triggers a stress response associated with changes in hemodynamic variables [10].

Orotracheal intubation can activate additional receptors that trigger enhanced hemodynamic and epinephrine responses, as well as some vagal inhibition of the heart, leading to various cardiovascular changes. These changes are usually temporary, variable, and unpredictable. The average increase in heart rate has been reported to be 23 beats, and the increase in blood pressure by 53/54 mmHg more than baseline. Additionally, the left ventricular ejection fraction may decrease by approximately 20% less than baseline [4].

Precipitating factors of the pressor response:

Light planes of anesthesia, prolonged time for the procedure, elevation of vagally innervated posterior part of epiglottis by straight/Miller blade, anatomically difficult view, greater force used to displace the tongue and more manipulations/attempts at laryngoscopy and intubation all over are precipitating factors of pressor response [11].

Prolonged intubation time can also contribute to the stress response to laryngoscopy and intubation. Additionally, rapid first-attempt success is of particular importance in minimizing the risk of stress response [12].

The cardiovascular responses to laryngoscopy with different blade designs show that the Macintosh blade compresses the soft tissue of the anterior epi-pharynx more than the straight blade laryngoscope, resulting in more increase in heart rate and blood pressure but laryngoscopy with the McCoy blade produces minimal hemodynamic changes and does not result in any significant increase in plasma noradrenaline concentration [13].

Stress responses during laryngoscopy are influenced by the forces applied during the procedure, which cause mechanical stimulation of the airway. When laryngoscopy is difficult, the force required to obtain a clear view of the glottis is increased, resulting in an increased stress response [14].

The duration of laryngoscopy, the forces applied parallel to the axis of the handle and the increased stretching of the tissues were found to be responsible for the severity of the hemodynamic perturbations. [15].

Prevention of pressor response:

The cardiovascular responses to airway maneuvers can be minimized by limiting airway proprioceptor stimulation. This can be achieved by starting with manipulation of the larynx itself, such as applying cricoid cartilage pressure with a posterior force of 4.5 kg to prevent regurgitation of gastric contents or to facilitate laryngeal visualization [16].

The magnitude of the pressor response to laryngoscopy and intubation is proportional to the duration of the procedure. A longer intubation time should result in a higher stress response, but laryngoscopy duration less than 30 seconds does not have any effect on the hemodynamic response [17].

Regional nerve blocks involving the sensory pathways from the airway prevent hemodynamic responses to intubation. The superior laryngeal nerve (SLN) innervates the superior surface of the larynx, and the glossopharyngeal nerve innervates the oropharynx. Depositing local anesthetic on each cornu of the hyoid bone can block the SLN. Blockage of the glossopharyngeal nerve at the tonsillar pillars (sensory distribution above the level of the epiglottis) potentiates this effect by decreasing the stimulus of laryngoscopy [18].

Inhalational anesthetics are used to block the cardiovascular response to endotracheal intubation. However, the dose of volatile anesthetic required to achieve this effect is inordinately high, resulting in profound cardiovascular depression before endotracheal intubation [19].

Using pharmacological agents like intravenous opioids, beta-adrenergic blockers, calcium channel blockers, α2 agonist, local anesthetics, and topical sprays, volatile agents. Also, intranasal and nebulizer have been used for prevention of this stress response with variable success [20,21].

Nebulized drug administration is highly preferred over intranasal administration, as it prevents transient nasal irritation, cough, vocal cord irritation or laryngospasm [22].

Nebulization

It is the process of medication administration via inhalation. It utilizes a nebulizer which transports medications to the lungs by means of mist inhalation. Nebulization creates a mist of drug particles that can be inhaled via a face mask or mouthpiece soothing the inflamed airways. A nebulizer is a device that can convert a drug from a solution into an aerosol form by means of a compressor or compressed gas source [23].

Nebulizers are widely used for the inhalation of drug solutions in a variety of respiratory diseases; Nebulization is primarily preferred for safety and ease of administration to the patient and has the benefit of delivery of the drug to the lower airway with little chance of aspiration [24,25].

During nebulization, the liquid is broken up into droplets by the compressed air, and it produces large particles (10–25 μm), which mostly deposit in mouth and throat, and smaller particles (5–10 μm), which deposit in a

transition from mouth to airway. The efficacy of nebulizer therapy is influenced by a great number of factors, including the design of the device, the characteristics of the drug solution and maintenance and disinfection procedures [26].

Types of nebulizers:

I- Mechanical

(A) Soft mist inhaler: This type provides a metered dose to the user, as the liquid bottom of the inhaler is rotated clockwise 180 degrees by hand, adding a buildup tension into a spring around the flexible liquid container. When the user activates the bottom of the inhaler, the energy from the spring is released and imposes pressure on the flexible liquid container, causing liquid to spray out of 2 nozzles, thus forming a soft mist to be inhaled. The device features no gas propellant and no need for battery/power to operate. The average droplet size in the mist was measured to a somewhat disappointing 5.8 micrometers, which could indicate some potential efficiency problems for the inhaled medicine to reach the lungs [27].

(B) Human powered nebulizer: The human-powered nebulizer (HPN) is designed to provide relief to patients suffering from respiratory diseases such as asthma, TB or chronic obstructive pulmonary disease in areas with limited access to electricity [28].

II-Electrical:

(A) Jet nebulizer: Jet nebulizers utilize compressed air to aerosolize drug solutions while ultrasonic nebulizers employ high-frequency sound waves. Jet nebulizers have evolved from conventional designs to open-vent and breath-assisted types. In jet nebulizers, the droplet generator is a two-fluid atomizer, and different designs based on the same principle are used. For a typical jet nebulizer, compressed air passes through a narrow hole and entrains the drug solution from one or more capillaries mainly through momentum transfer. The complex liquid break-up process depends on the nozzle design and typically involves the turbulent rupture of the unstable liquid column and secondary droplet break up. In its simplest form, the air impinges directly on a solid jet of liquid, and large droplets impact on one or more baffles to refine the droplet size distribution to the desired range for inhalation. Only smaller droplets can follow the streamlines of the air and pass the baffle [29].

(B) Ultrasonic wave nebulizer: The technology inside an ultrasonic wave nebulizer is to have an electronic oscillator generate a high frequency ultrasonic wave, which causes the mechanical vibration of a piezoelectric element. This vibrating element is in contact with a liquid reservoir and its high frequency vibration is sufficient to produce a vapor mist, as they create aerosols from ultrasonic vibration instead of using a heavy air compressor [30].

(C) Vibrating mesh nebulizer: A new significant innovation was made in the nebulizer market around 2005, with creation of the ultrasonic Vibrating Mesh Technology (VMT). With this technology a mesh or membrane with 1000-7000 laser drilled holes vibrates at the top of the liquid reservoir, and thereby pressures out a mist of very fine droplets through the holes. This technology is more efficient than having a vibrating piezoelectric element at the bottom of the liquid reservoir, and thereby shorter treatment times are also achieved. The old problems found with the ultrasonic wave nebulizer, having too much liquid waste and undesired heating of the medical liquid, have also been solved by the new vibrating mesh nebulizers [30].

Ketamine

Ketamine is a derivative of phenycyclidine and is a chiral compound. It can be presented as a racemic mixture or as the single S(+) enantiomer, which is 2 to 3 times more potent than the R (-) enantiomer as in. Most pharmaceutical preparations of ketamine are racemic. The more active enantiomer, S-ketamine, is available for medical use, while the less active enantiomer R-ketamine is not commonly used in medicine [31].

Ketamine has multiple side effects. Dilated pupils, nystagmus, lacrimation, and increased muscle tone are common. It increases salivation which can lead to laryngospasm and airway obstruction [32].

Ketamine increases intraocular pressure and intracerebral pressure, so it should be avoided in patients with intracranial mass effect or increased ICP [33].

The increase of circulating catecholamines associated with ketamine results in the stimulation of the cardiovascular system causing elevations in blood pressure, heart rate, cardiac output, and myocardial oxygen

consumption These cardiovascular effects are not related to dose. Caution should be used in patients with existing hypertension or ischemic heart disease [34].

NMDA receptor antagonists can also cause unfavorable psychological reactions including vivid dreams, a sense of detachment from the body, illusions, and hallucinations [34].

The visual disturbances may be accompanied by excitement, confusion, euphoria, or fear. Pediatric patients have lower incidence of psychological adverse reactions. Both the psychological and cardiovascular effects can be reduced by the use of benzodiazepines [33].

Contraindication of Ketamine:

It is contraindicated in those who have shown prior hypersensitivity to the drug. It is not recommended for use during breastfeeding as it is unknown if this medication passes into breast milk Care must be used in patients who are intoxicated with ethanol due to additive sedation. It is contraindicated in patients with schizophrenia due to the potential for exacerbating the underlying condition, in patients with underlying conditions in which increased blood pressure would pose a risk of complications such as aortic dissection, uncontrolled hypertension, myocardial infarction, or aneurysms [35]. In patients with cerebrospinal fluid (CSF) elevations, the use of ketamine is controversial due to questionable elevations of the CSF caused by ketamine.

Using Ketamine as a nebulizer:

Pharmacokinetic properties of inhaled ketamine have been studied officially in pevious studies. It can be given in dose 25-50 mg nebulization to reduce post operative sore throat (POST) [36].

Ketamine has been used successfully to treat acute pain in intranasal form. Nebulized ketamine as an analgesic bypassing first pass metabolism and without the need for intravenous access, used to decrease the need for rescue analgesia during PACU care [37].

Nebulized form of ketamine bypass first pass metabolism, so it decreases load on liver and kidney that is done by most of analgesics used as NSAIDS and opioids [38].

Delivery of ketamine by inhalation is safe, accessible, and simple method. Advantages of this route include the possibility of ketamine administration outside the hospital setting in cases if no I.V. access line is required [39].

Magnesium Sulphate

Magnesium is the fourth most common ion in the body and plays a crucial role in various cellular processes, including protein synthesis, neuromuscular function, and the stability of nucleic acids. It acts as a cofactor in these processes and regulates other electrolytes such as calcium and sodium. Magnesium is a calcium antagonist, non-competitive inhibitor of calcium channels with inositol triphosphate, and modulates sodium and potassium currents. This interference with transmembrane potential makes it a central nervous system depressant, antagonizing N-methyl-D-aspartate (NMDA) and inhibiting the release of catecholamines [40].

Magnesium is essential for many biochemical reactions in the body, and its deficiency can lead to clinically important consequences during anesthesia or in the intensive care unit, some of its properties may be of value in certain areas of anesthetic practice. The physiological role of magnesium is due to its calcium channel blocking properties at smooth muscle, skeletal muscle, and conduction system levels. Its analgesic properties are attributed to NMDA receptor blocking action. Magnesium is a cost-effective, widely used drug with multidisciplinary applications [41].

Magnesium Sulphate Chemistry:

Magnesium sulfate, also known as Epsom salt, is a chemical substance with the formula MgSO4. It occurs in three hydration states: monohydrate, heptahydrate, and anhydrous. The product is made up of two manganese cations and sulfate anions. Sulfur is placed in the center of the molecule, and the oxygen atoms are surrounding the sulfur atom with a double bond or a single bond. This chemical substance adopts an orthorhombic crystalline structure [42].

Normal serum Mg concentration is 1.5–2 mEq/L. In the body, Mg exists as a cation, or bound to albumin. It is physiologically active in its ionized form and able to pass rapidly through cell membranes (therefore, extracellular levels reflect intracellular levels) [42].

Pharmacodynamic [43]:

Activation of sodium–potassium ATPase pump: Magnesium plays a crucial role in the activation of the sodium–potassium ATPase pump, which is responsible for maintaining the sodium and potassium balance in the body. Inhibition of this pump occurs with high serum mg concentrations.

Competitive antagonism of calcium channels: Magnesium exhibits competitive antagonism towards calcium channels, particularly those in smooth muscle, skeletal muscle, and the conduction system. This property is responsible for its physiological effects on muscle relaxation and the cardiovascular system.

Non-competitive antagonism of N-methyl-D-aspartate (NMDA) receptors: Magnesium also displays non-competitive antagonism towards NMDA receptors, which are involved in the transmission of excitatory signals in the central nervous system. This property contributes to its analgesic effects and the suppression of excessive glutamate release.

Blocking presynaptic acetylcholine release: Magnesium blocks the release of acetylcholine from presynaptic nerve terminals, which results in decreased cholinergic transmission and muscle contractions.

Increasing postsynaptic action potential threshold: Magnesium increases the threshold for action potentials in postsynaptic cells, which leads to a decrease in the excitability of the central nervous system.

Blocking catecholamine release from adrenal glands and adrenergic nerve terminals: Magnesium blocks the release of catecholamines from the adrenal glands and adrenergic nerve terminals, resulting in decreased sympathetic outflow and blood pressure.

Decreasing cytokine release: Magnesium has been shown to decrease the release of inflammatory cytokines such as IL-1, IL-6, TNF-a, and substance P. This property contributes to its anti-inflammatory effects and the suppression of excessive immune responses.

Heart: Sinoatrial and atrioventricular (AV) block, PR prolongation, and QRS widening.

Platelets: Inhibition of platelet aggregation (high serum Mg concentrations).

So the pharmacological effects of Mg sulphate are:

Central nervous system: Sedation, analgesia (cerebral and neuraxial), and cerebral vasodilation. Magnesium sulfate exerts its central nervous system effects by blocking NMDA receptors and increasing the threshold for action potentials in postsynaptic cells. This results in decreased cholinergic transmission, muscle contractions, and excessive glutamate release [44].

Heart: Antiarrhythmic effects, systemic, pulmonary, and coronary vasodilation, and nonstriated muscle arterial vasodilation. Magnesium sulfate's cardiovascular effects are primarily due to its calcium channel blocking properties, which lead to a decrease in calcium influx and the relaxation of smooth muscle cells in blood vessels. This results in increased blood flow and a reduced risk of thrombosis [45].

Bronchodilation: Magnesium sulfate has been shown to cause bronchodilation by relaxing smooth muscle cells in the airways. This property may be beneficial in the treatment of asthma and other respiratory disorders [46].

Tocolysis: Magnesium sulfate is commonly used to inhibit uterine contractions and prevent preterm labor. Its effects on calcium channels and the central nervous system contribute to its tocolytic properties [47].

Striated muscle: Muscle relaxation, particularly in the context of anesthesia and sedation. Magnesium sulfate's ability to block calcium channels and inhibit the release of acetylcholine from presynaptic nerve terminals results in decreased cholinergic transmission and muscle contractions [48].

Inflammation: Inflammatory response modulation, including the suppression of excessive cytokine release and the promotion of membrane stabilization. Magnesium sulfate's anti-inflammatory effects may be beneficial in the treatment of various inflammatory disorders and the prevention of excessive immune responses [49].

Metabolism: Membrane stabilization and the promotion of proper cell function. Magnesium plays a crucial role in various biochemical reactions and is essential for the maintenance of proper metabolic function [50].

Platelets: Antiaggregating, particularly at very high doses. Magnesium sulfate's ability to inhibit platelet aggregation may be beneficial in the prevention of thrombosis and the maintenance of proper blood flow [51].
Pharmacokinetic: If given intravenous administration, the onset of action is immediate and the duration approximately 30 minutes. If given intramuscular administration the onset of action occurs after approximately one hour and the duration of action is 3-4 hours.
Distribution: Protein bound: 30% Extracellular distribution: 1-2%
Excretion: Magnesium sulfate is excreted by the kidneys with small amounts being excreted in breast milk and saliva [52].

Magnesium sulphate in anesthesia:

Magnesium sulfate is used in anesthesia and sedation most frequently and in obstetrics. The high frequency of using magnesium attention being paid to this drug, as well as the introduction of multimodal analgesia and anesthesia techniques [53].
Magnesium sulphate as analgesia:
Magnesium is an intracellular cation that contributes to the adjustment of enzyme reactions and the regulation of ionic channels. It is also being used for anesthetic purposes due to its blocking effect on calcium channels. Although its mechanism of action is not fully understood, interference in N-methyl-D-aspartate (NMDA) receptor regulations is believed to play a significant role. In the central nervous system, NMDA receptors are involved in the transmission of excitatory signals. Magnesium displays non-competitive antagonism towards NMDA receptors, which helps to suppress excessive glutamate release and maintain a balance in neurotransmitter levels. This property contributes to its analgesic effects and the suppression of excessive glutamate release. In addition to its effects on NMDA receptors, Mg sulphate also modulates the activity of various G-protein-coupled receptors (GPCRs), which are involved in the regulation of smooth muscle tone, inflammation, and immune response [54].

Uses applications of magnesium sulfate:

Magnesium sulfate is used an adjunct in anesthesia reduces intraoperative consumption of anesthetics [55].
Studies in clinical practice have shown that magnesium has inhibitory effects on the release of catecholamines and can improve hemodynamic control during laryngoscopy [56,57].
It's used in pneumoperitoneum insufflation in laparoscopic surgeries [58].
Magnesium sulfate also reduces levels of noradrenaline and vasopressin during anesthesia [59].
Magnesium increases microcirculation in cerebral blood flow which prevents vasospasm in patients suffering from aneurysmal subarachnoid hemorrhage [60].
Using of magnesium sulfate with nondepolarizing neuromuscular blockers leads to prolongation of its mechanism of action [61].
magnesium sulfate nebulization has a significant effect to attenuate the stress response to Endotracheal intubation in the form of attenuating increase of Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Heart Rate (HR), and Blood Glucose level [62].
Nebulized MgSO4 had beneficial effects in the treatment of infants and children with wheezy chest [63].
Magnesium Sulphate (MgSO4) Nebulization versus Salbutamol Nebulization in Acute Asthmatic Attacks in Adults [64].

Magnesium Sulfate Toxicity:

Hypermagnesemia, or high levels of magnesium in the plasma, is relatively uncommon and is often associated with renal failure, particularly during therapeutic administration of magnesium-containing drugs or other treatment-related causes. For example, patients treated for eclampsia may experience hypermagnesemia due to the use of mg sulfate to control seizures [65].
The toxic effects of magnesium are indeed linked to the levels (mEq/liters) found in the serum. As the levels rise, different symptoms manifest, and the fatality of those symptoms is proportional to the levels of magnesium found.

At 5 to 10 mEq/L, patients will begin to develop ECG changes, such as a prolonged PR interval and a widened QRS. At 10 mEq/L, there will be a loss of deep tendon reflexes and muscle weakness. At 15 mEq/L, signs of abnormal conductivity will surface, such as SA/AV node block. Additionally, patients will experience respiratory paralysis. At 20 mEq/L or higher, may cause cardiac arrest as in [66].

Treatment of Magnesium Sulfate Toxicity:

The treatment approach for hypermagnesemia depends on the severity of the electrolyte imbalance and the patient's clinical presentation. Mild cases may only require discontinuation of the source of Mg and close monitoring, while severe cases may require immediate treatment to lower the plasma Mg levels and provide supportive care [67].

Patients receiving parenteral magnesium should be closely monitored, and those with renal failure should avoid magnesium containing medications. If renal functions are normal, discontinuing therapy often leads to a rapid recovery of magnesium levels, which can be further aided by fluid therapy and diuretics. In cases of renal failure or severe systemic effects, hemodialysis or filtration may be necessary. IV calcium gluconate (2.5-5 mmol) can counteract the effects of magnesium and is therefore useful in the immediate management of patients with severe hypermagnesemia. This should be followed by inducing diuresis or dialysis [68].

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