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Nebulized Lidocaine in COVID-19, An Hypothesis

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ABSTRACT

Coronavirus Diseases-2019 (COVID-19) has caused a large global outbreak and has been declared as a pandemic by the World Health Organization (WHO). It has been proposed that COVID-19-related hyperinflammation and dysregulated immune response might play a critical role in developing a cytokine storm which usually progresses to a life-threatening acute lung injury or acute respiratory distress syndrome in infected individuals. Lidocaine, a local analgesic and anti-arrhythmic, is known for its anti-inflammatory actions and has been used to reduce cough and improve respiratory symptoms in severe asthmatic patients. It has a demonstrated safety profile. It is proposed that nebulized lidocaine might be beneficial in reducing cytokines, protecting patients' lungs and improving outcomes in COVID-19 patients when administered via inhalation as an adjunctive treatment for severe respiratory symptoms in patients fighting the novel Coronavirus. Additional investigation is warranted.

Introduction

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes Coronavirus Diseases-2019 (COVID-19) has produced a large global outbreak which has been declared as a pandemic by the World Health Organization (WHO) [1]. Its emergence follows the same pattern as previous pandemics: emergence from a zoonotic pathogen pool in an area in which changes in human population density, wildlife diversity, and local behavioral and socioeconomic realities predispose animal to human spread of disease [2]. In less than one year, COVID-19 has had a devastating health and economic impact worldwide, but the ultimate effect remains unknown [3]. There continues to be no available vaccine, and current preventative strategies are non-specific [4]. Similarly, there are no specific treatments, and current interventions are predominantly supportive [5]. Since treatment is nonspecific, multiple approaches will need to be combined to optimize outcome.

Role of inflammatory response in respiratory distress

Early literature suggests that over 20% of infected individuals with coronavirus-related pneumonia will experience acute respiratory distress syndrome (ARDS) [6]. Among patients with pneumonia caused by COVID-19, fever was the most common symptom, followed by cough and dyspnea as well as chest pain in severe cases [7]. ARDS in COVID-19 patients is believed to have a similar pathology to related coronavirus infections, SARS and Middle Eastern respiratory syndrome (MERS), and involve an excessive immune response which might lead to death of epithelial cells and endothelial cells, followed by activation of abnormal T-cells and macrophages [8–9]. This leads to a severe inflammatory response which induces a change of vascular permeability, causing acute pulmonary edema with the formation of hyaline membranes and a diffuse thickening of the alveolar wall [8–9]. Cellular apoptosis and amplified immune response activate a cytokine storm in the lower airway with extreme rise in plasma cytokines and chemokines including interleukins (IL-1, IL-2, IL-6, IL-7, IL-8, IL-9, and IL-10), fibroblast growth factor (FGF), granulocyte–macrophage colony stimulating factor (GM-CSF), IFN-γ, granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), platelet derived growth factor (PDGF), tumor necrosis factor (TNF-α) and vascular endothelial growth factor (VEGF) [10,11].

A rapid and controlled immune response is the first line of defense against viral infections; however, a dysregulated and extensive immune response may worsen outcome by mediating extensive pulmonary pathology, leading to massive infiltration of neutrophils and macrophages, excessive production of cytokines, and diffuse alveolar damage [12], generating a vicious cycle for coronavirus-related ARDS [9]. COVID-19 virus is known to bind and gain cellular entry via angiotensin converting enzyme 2 (ACE2) receptors, which are highly expressed in the lung [13]. Lymphocytopenia is one of the most notable markers of COVID-19, with markedly reduced yet hyperactivated numbers of

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$CD4^+$ T cells, $CD8^+$ T cells, B cells and natural killer (NK) cells [8]. It is speculated that lymphocytes are destroyed by the cytokine storm not by the virus itself since it is known that lymphocytes do not express ACE2 receptors which are the main target to COVID-19 [10]. It has been proposed that using anti-inflammatory agents and reduction in the cytokine response to COVID-19 induced hyper-inflammation may reduce the common respiratory distress and improve outcome [14].

Possible lidocaine effects on COVID-19

Lidocaine is known as a short-acting local anesthetic and an anti-arrhythmic agent which exerts inhibitory actions on voltage-gated sodium (Na^+) channels and calcium (Ca^{2+}) channels [15]. Activation of some ionic channels, including Ca^{2+}, potassium (K^+), and chloride (Cl^-) channels, play a critical role in T-cell activation [16]. A study suggests that activation of voltage-sensitive and voltage-gated Na^+ channels is a crucial step in permitting an adequate influx of Na^+ and preserving a high and sustained Ca^{2+} concentration during the process of T-cell activation [17]. Tanaka et al in an in vitro model, showed that inhalational doses of lidocaine have immunoregulatory effects on T cells derived from patients with allergic asthma by directly inhibiting cytokine production and the proliferative response through blockade of of Ca^{2+} and Na^+ channels [18].

Recently, some preliminary studies have demonstrated anti-inflammatory actions for local anesthetics including lidocaine [19]. The mechanism of its anti-inflammatory action is still unclear; however, it has been hypothesized that lidocaine might regulate cellular metabolic activity, migration, exocytosis and phagocytosis by reversibly interacting with membrane proteins and lipids [19]. Lidocaine was found to attenuate the inflammatory response in animals by decreasing polymorphonuclear granulocytes (PMNs) accumulation in the lung [20]. Cytokine release, respiratory burst, and phagocytosis are important functions of macrophages, and it was demonstrated that these processes are sensitive to intracellular pH changes which are regulated by vacuolar-type-H^+ translocating adenosine triphosphatase and an Na^+-H^+ exchanger (NHE) [21]; lidocaine inhibits NHE in human PMNs in vitro which indicates a possible mechanism of attenuating cytokine release by lidocaine [22]. The anti-inflammatory properties of lidocaine encouraged physicians to introduce it into clinical practice and lidocaine has been successfully used in some inflammatory diseases and conditions such as burn injuries, interstitial cystitis, ulcerative proctitis, arthritis and herpes simplex infections [19].

Animal studies highlight the potential benefits of lidocaine. Studies involving animal models have showed beneficial effects of lidocaine on lung injury. Lidocaine infusion attenuated Escherichia coli endotoxin-induced lung injury and significantly reduced lung edema, leukocyte counts and the release of various inflammatory mediators [23]. Similar studies were conducted on pancreatic enzymes-induced, HCl-induced and bleomycin-induced lung injury in animals and showed that lidocaine attenuated morphologic and histologic lung damage [20,24–25]. In a murine model of asthma, lidocaine nebulization significantly reduces the levels of cytokines IL-4, IL-5, IL-13 in lung tissues in addition to reduction in parabronchial fibrosis [26]. Plasma levels of IL-6 and IL-8 concentrations in bronchoalveolar fluids were reduced in animals infused with lidocaine [21]. Additionally, lidocaine was found to decrease cytokine-induced cell injury *in-vitro* [27]. A recent study has demonstrated that inflammatory markers IL1, and IL-6, interferon-g, and tumor necrosis factor α (TNFα) were significantly reduced following administration of intravenous lidocaine in patients undergoing laparoscopic cholecystectomies [28]. There are promising early results that agents that antagonize IL-1 and IL-6 may be of specific utility in patients infected with COVID-19 virus. Malik et al., proposed a similar hypothesis, that lidocaine might be of use in COVID-related lung injury through a possible antiviral effect and by targeting ion channels, particularly stretch activating ion channels in lungs [41].

Nebulized lidocaine has showed a promising efficacy and safety of lidocaine in suppressing cough [29], improving pulmonary functions and reducing the need for using corticosteroids in asthmatic patients [30–31]. If this observation is generalizable, one would expect that lidocaine might have a role in treating respiratory symptoms in patients with COVID-19 by reducing cough and numb patients' chest pain. Nebulized lidocaine appears to be a possible option for improving COVID-19 related lung injury by reducing cytokine storms that usually occur with COVID-19 which would theoretically reverse ARDS.

Dosage and safety of nebulized lidocaine

Nebulized solutions varying in concentration from 1% to 4% have been studied and used without major side effects on patients [29]. Studies have found that large doses of lidocaine inhalation up to 575 mg are quite safe [29]. Lidocaine has short half-life; using nebulized lidocaine every 4–6 h in a dose of 4% Lidocaine in 2 ml saline will achieve between 320 and 480 mg of a daily dose of lidocaine. Studies have been done to evaluate the plasma level of nebulized lidocaine; 400–525 mg of nebulized lidocaine produced peak levels of 1.1 and 1.4 mcg/ml, respectively, which is far below the 5 mcg/ml level associated with toxicity [32–33]. Lidocaine has been safely administered to patients with COVID-19 infection to manage cough during intubation and extubation [34], and prevent potential cardiac complications of chloroquine, hydroxychloroquine or azithromycin [35].

Common adverse effects are unpleasant taste, throat and mouth irritation, and oropharyngeal numbness [36]. Numbness of the oropharynx with lidocaine use could theoretically predispose patients to micro-aspiration and subsequently secondary bacterial infections; however, earlier studies demonstrated inhibitory actions of lidocaine on various strains of bacteria which suggests a prophylactic rule of lidocaine against bacterial infections [19,37].

The risk of bronchoconstriction is still controversial. Some studies have showed that extensive use of 10% lidocaine infusion may cause reflex bronchoconstriction in asthmatics [38–39], other studies found no effect on the airways [36,40] and it appears that route of administration may be important in this adverse outcome (nebulized being safer). If patients suffer from asthma or hyperreactive airway, it may be reasonable to pre-administer a bronchodilator which usually prevents the potential of a bronchospasm induced by lidocaine [39].

Conclusion

Lidocaine inhalation has anti-inflammatory effects that are predicted to reduce inflammatory cytokines which appear to be a major problem in COVID-19-related cytokine storm [41]. Given the complications and risks of the available anti-inflammatory agents, lidocaine, with its relatively benign side effect profile, would be a promising adjunctive treatment for COVID-19 patients with severe respiratory symptoms and those who develop a cytokine storm. Additional research is warranted to further define its efficacy and safety in treating severe ARDS in COVID-19 virus-infected patients.

Declaration of competing interest

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CRediT authorship contribution statement

Ziad A. Ali: Resources, Writing - original draft, Writing - review & editing. **Rif S. El-Mallakh:** Writing - original draft, Writing - review & editing, Supervision.

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