Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Anti-inflammatory aspects of Lidocaine: a neglected therapeutic stance for COVID-19

To,

The editor

Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has emerged as one of the prime global health threats of the decade. The fledging outbreak was registered a pandemic by the World Health Organization (WHO) on March 11, 2020.[1] In less than one year, the atrocities of the disease have created a significant void in the worldwide economic stability, especially by grinding the healthcare industry. The unavailability of a vaccine remains a loophole in the disease management, which is why the use of established non-specific drugs such as hydroxychloroquine and azithromycin has come into play. Predominantly, supportive treatment is working as the backbone of the current COVID-19 management. Since there is a lack of specific therapy, older drugs deemed irrelevant need to be brought into perspective and re-evaluated for their therapeutic effects against COVID-19. One such drug is lidocaine, whose therapeutic advantages need emphasis. The benefits of lidocaine already exist in literature; however, the subject needs to be elucidated so that the drug can be utilized to combat COVID-19.

Inflammatory sequelae of COVID-19

The exaggerated immune response of COVID-19 pathologically resembles that of other coronavirus infections, like Severe Acute Respiratory Syndrome (SARS). In response to the amplified viral replication in human cells, the body's immune response taskforce is activated, and multiple cells such as T lymphocytes, macrophages, and neutrophils are summoned to fight the infection. It has been recently proposed that there might be a substantial role of neutrophils in causing mortality and multi-organ dysfunction in COVID-19.[2] Evidence of netosis (presence of neutrophil extracellular traps, namely NETS) has been found in COVID-19. In one study, citrullinated histone H3 (Cit-H3), a specific biomarker of NETS, was elevated in hospitalized COVID-19 patients.[3]

COVID-19 pathophysiology comprises dominantly of a cytokine storm, which is characterized by a surge of plasma cytokines and chemokines, especially interleukins (IL). IL-1, IL-2, IL-6, IL-7, IL-8, IL-9, and IL-10 are involved in the inflammatory cascade. Furthermore, NETS also trigger IL-1 release from macrophages, which potentiates IL-6 secretion.[4]

Lidocaine use in COVID-19

Lidocaine is an amide-based, short-acting local anesthetic. It is also recognized commonly as a class 1b antiarrhythmic drug. The mechanism of action of the drug includes blocking the voltage-gated sodium and calcium channels, ultimately repolarizing them. Strong evidence exists regarding the proportional effect of sodium and calcium channel activation to T cell and cytokine proliferation, which affirms that lidocaine has a role in tempering excess immune responses.[5] This corroborates the anti-inflammatory properties of lidocaine.

The cardioprotective effects of the drug are well-acclaimed. Gopinathannair et al. concluded in his study that 64 out of 441 COVID-19 patients used lidocaine/mexiletine against the arrhythmic manifestations of the infection.[6] Furthermore, in one study, intravenous lidocaine was evaluated for its role in QT prolongation as a combination therapy with azithromycin and chloroquine/hydroxychloroquine.[7] Promising results were obtained as lidocaine dampened QT prolongation associated with the aforementioned drugs.

Lidocaine is being actively administered in COVID-19 patients to depress cough during intubation, and extubation.[8] Cough is a characteristic symptom of the infection that is prone to exacerbation on airway instrumentation. Drugs such as opioids, when given before inducing anesthesia, can spike a cough activity. A single intravenous dose of lidocaine, which is readily available in hospital setups, can prevent such an occurrence, without causing significant side effects. Nebulized lidocaine is also being considered for use in COVID-19 because of its safer profile and efficacy in suppressing cough.

Anti-inflammatory properties of Lidocaine

Lidocaine is a potent anti-inflammatory drug, so much so that its anti-inflammatory characteristics are compared with steroids and non-steroidal anti-inflammatory drugs (NSAIDs).[9] The definite anti-inflammatory mechanism of lidocaine remains vague; however, it is presumed that the drug affects a multitude of inflammatory processes such as phagocytosis, migration, exocytosis, and cellular metabolism. In vitro experiments on human polymorphonuclear granulocytes suggested that lidocaine inhibited the membrane-ion transporters, therefore, dysregulating the cellular pH levels and eventually depressing the cytokine release.[5] The anti-inflammatory properties of lidocaine are increasingly being acknowledged, and practitioners are frequently utilizing the drug against a vast number of inflammatory conditions such as in burn wounds, herpes simplex, ulcerative proctitis, and arthritis.[5]

Another study concluded that the administration of intravenous lidocaine effectively decreased the inflammatory markers in patients undergoing laparoscopic cholecystectomies; the most significant markers being IL-1, IL-6, interferon-gamma, and tumor necrosis factor α.[10] These results emphasize on lidocaine's antagonizing actions on IL-1 and IL-6, which are the most significant inflammatory markers of

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the COVID-19 infection. Although these findings are presumptive, they may be a breakthrough for COVID-19 management, especially if more clinical trials are centered around the hypothesis.

A prospective randomized controlled trial evaluated the outcome of lidocaine administration in patients undergoing surgery.[11] A marked positive influence of lidocaine infusion was seen on reducing the specific inflammatory markers of netosis (primarily Cit-H3). Patients who received a lidocaine infusion for anesthetic induction had significantly low levels of plasma Cit-H3 compared to the control group that did not receive the drug. Netosis is a key finding in hospitalized COVID-19 patients. Thus, lidocaine's efficacy in disrupting netosis in surgical patients is quite a development, which paves the way for repurposing it for COVID-19 subjects. In this way, lidocaine can attenuate the intense cytokine storm in patients infected with SARS-CoV-2, hence obstructing severe disease progression.

Low side effect profile of Lidocaine

Lidocaine is one of the safest anesthetics available, irrespective of how it is administered.[5] Nebulized lidocaine solutions have no major side-effects and are administered in concentrations ranging between 1% to 4%. Large doses of inhalational lidocaine can also be given, as the risk of adverse effects is minimal. Minor side effects associated with lidocaine use include unpleasant taste, throat irritation, and oropharyngeal numbness.[5]

Conclusion

Lidocaine, irrespective of the way it is administered, can play a pivotal role in the management of COVID-19. It has potent anti-inflammatory effects that can help mitigate the pathogenic cytokine storm associated with the infection. With its benign side-effect profile, it can be easily included in the treatment regimen for impeding the development of severe respiratory symptoms in patients infected with SARS-CoV-2. Clinical trials and scientific evaluation of the drug against COVID-19 need encouragement. We propose that the anti-inflammatory wonders of lidocaine in SARS-CoV-2 infected individuals is a subject that needs probing. With its multiple benefits, the drug can likely emerge as one of the vital therapies against COVID-19 infection.

Author contributions

Dr Maab and Dr Mustafa contributed to the conception or design of the work. Dr. Arshad Ali contributed to the literature review. Dr. Maab drafted the manuscript. Dr. Mustafa and Dr. Arshad Ali critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring accuracy of the manuscript.

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Declarations of Competing Interest

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