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Review Article

Enhancement of Innate Immunity to COVID-19 with Natural Measures

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ABSTRACT

The strength of Corona virus disease 2019 (COVID-19) is the fact that it is a novel virus to humans. Being a neoteric virus yields a significant advantage as the person infected possess no immunity to the pathogen. The most significant protection against a new viral infection is the ancient innate immune system. When the virus invades our cells, receptors in the cytoplasm recognize the foreign intruder and induce innate immune responses to block replication of the virus. A robust response is critical as it takes three to five days to generate the beginnings of an adaptive immune response. The front line innate immune response is often powerful enough to eliminate the virus before the development of more severe late-phase infection, which relies on acquired immunity for resolution. A recent scientific discovery demonstrates a natural, safe, and accessible self-administered procedure that enhances our innate immunity. Non-myeloid epithelial cells are capable of producing the viricidal substance hypochlorous acid (HOCL). The amount of HOCL generated is dependent on the concentration of intracellular chloride that is available. *In vitro*, saline exposure of epithelial cells infected with coronavirus significantly reduced viral replication. *In vivo*, hypertonic saline nasal irrigation and gargle (HSNIG) in patients who had upper respiratory infections (URI) caused by coronavirus significantly reduced the duration and severity of the URI compared to similarly infected patients treated with the standard of care. HSNIG can suppress viral replication of COVID-19 mitigating the spread during the asymptomatic phase and reducing the risk of an asymptomatic or symptomatic case progressing to a severe infection.

Keywords: Innate immunity; Hypochlorous acid (HOCL); Corona virus disease 2019 (COVID-19); Hypertonic saline nasal irrigation and gargle (HSNIG); Angiotensin-converting enzyme-2 receptor (ACE2)

INTRODUCTION

Innate immunity provides first-line protection against invading pathogens. It is ancient and present in all living organisms. When a foreign microbe invades a cell, cytoplasmic receptors recognize this intrusion and immediately activate the immune response to prevent the replication of the pathogen. An additional innate defensive mechanism is the mobilization of natural killer (NK) cells that can recognize virus infected cells and immediately kill them to eliminate the potential for rapid viral spread [1]. Vertebrates possess a supplemental form of immunity called adaptive or acquired immunity. This form of protection, unlike innate immunity, has memory. The adaptive arm of the immune system enables a rapid and more comprehensive immune response to a repeated infection. The synergy between innate and acquired immunity generates substantial security when a recurrent infection occurs [2].

The lack of an immediate collaboration between innate and adaptive immunity for suppression of an infection is a tremendous advantage for any novel infection. When a de novo infection occurs, there is only one branch of the immune system that can defend against it. Innate immunity is that initial and exclusive early protection. Innate immunity activates responses to quell the replication of the microbe and to stimulate the creation of acquired immunity to the pathogen (memory). If innate immunity is unsuccessful in eliminating the infection, complementary action by acquired immunity is critical. It is important to remember that adaptive immunity is dependent on the effective function and delivery of viral antigens by cellular members of the innate immune response. Antigen presenting cells (APCs) from the innate response are required to present the invader to the adaptive arm of the immune system. Antigen presenting cells can be in the form of macrophages, dendritic cells, or neutrophils that have engaged and processed the viral invader. In general, it takes three to five days to generate active adaptive immunity. When innate immunity fails to abolish the infection, the evolution of an effective acquired immunity is necessary to resolve the late phase of infection. Therefore, efforts to enhance the immediate innate

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immune response to the degree it could potentially eradicate the microbe before acquired immunity is essential would be prudent [3]. A robust innate immune response against a novel infection would significantly blunt the pathogen's ability to capitalize on the absence of an immediate adaptive immune response.

INNATE IMMUNE ENHANCEMENT WITH HSNIG

Epithelial cells participate in innate immunity. Because these cells are non-myeloid, the belief has been that they are unable to generate the anti-microbial substance hypochlorous acid (HCOL). Many myeloid cells generate HOCL during the immune response to destroy bacteria and viruses. Dr. Ramalingam and colleagues recently found that epithelial cells can generate HOCL. They demonstrated that the amount of HOCL produced was dependent upon intracellular chloride levels. *In vitro* studies showed epithelial cells infected with viruses, including the human coronavirus 229E, were able to inhibit viral replication via intracellular production of HOCL. Exposing the cells to chloride from a concentrated saline solution improved the capability for inhibition by boosting the quantity of HOCL. This research demonstrated the potential to enhance the innate immune response of epithelial cells with Greater exposure to chloride which can safely be delivered with sodium chloride [4].

Dr. Ramalingam and colleagues performed a pilot study, the Edinburgh & Lothians Viral Intervention Study (ELVIS). The hypothesis revolved around boosting the effectiveness of nasopharyngeal epithelial cell innate immune response to viruses causing upper respiratory tract infections (URI) by bathing the cells in hypertonic saline. Theoretically, this could provide enough intracellular chloride for the epithelial cells to generate levels of HOCL to suppress viral replication. The primary outcome was to investigate if hypertonic saline nasal irrigation and gargle (HSNIG) is an acceptable therapy for patients with URI. Secondary outcomes included the effect of HSNIG on URI symptoms, URI duration, and viral shedding. Sixty-one healthy participants who had developed a URI within the last forty-eight hours were randomized half to HSNIG and half to the standard of care therapy. Nasal swab detected a virus in 73% of the patients, of which 56% were rhinovirus, and 31% were coronavirus. The hypertonic saline solution was 3.0% and made with Cornish sea salt. This concentration of saline is roughly 3X the concentration of physiologic saline and similar to the salinity of the ocean. The HSNIG was utilized a median of three times a day for a median of five days. Acceptability of the therapy was excellent with all participants stating it was easy to prepare, and 89% reporting the procedure was comfortable or moderately comfortable. It is remarkable that 86% also reported that the therapy was acceptable to perform outside of the home. HSNIG achieved a significant reduction in all symptoms and in the duration of the URI. HSNIG decreased viral shedding by 66%. The therapy also significantly reduced the spread of the URI to household contacts by 35%. The authors concluded that HSNIG is an acceptable treatment for viral URI and can diminish the severity and spread of URIs [5].

Due to the current COVID-19 pandemic, Dr. Ramalingam and colleagues performed a post-hoc analysis of ELVIS sorting out coronavirus induced URI. Fifteen people had coronavirus as the cause of their URI. Eight were in the control arm with two of those due to alpha-coronavirus and six due to beta-coronavirus which is the same type as COVID-19. In the HSNIG arm, four were due to alpha-coronavirus, and three were due to beta-coronavirus. HSNIG reduced the duration of the URI by 2.6 days with a p=0.054. The therapy also significantly reduced the duration of blocked nose, cough, and hoarseness. They conclude that a large trial is needed to prove definitively whether or not HSNIG is effective in COVID-19. The authors suggest HSNIG as a treatment of COVID-19 given the current science and the urgency to quell the COVID-19 pandemic [6].

Epithelial cells in nasopharynx represent the majority of cells first invaded by COVID-19. These cells are the primary initial target for invasion due to the simple anatomy of exposure for respiratory infections, plus the fact that COVID-19 has a high affinity for angiotensin-converting enzyme-2 (ACE2) receptor. ACE2 is the predominant receptor for COVID-19. The nasal epithelial cells have a relatively high expression of ACE2 [7]. Epithelial cells in salivary glands also have a relatively high expression of ACE2. In Rhesus Macaques, salivary epithelial cells were invaded early by SARS-CoV, which is a close relative of COVID-19 [8]. Substantial invasion of salivary epithelial cells in humans with COVID-19 may also be the case. Epithelial cells in the nasopharynx represent the front line of defense with the innate immune system. Nasopharyngeal epithelial cells' ability to significantly reduce viral replication would substantially mitigate the risk of viral shedding. Subsequently, reducing the spread of infection to others and the risk of progression to a more severe infection.

The above concept was recently reinforced by an excellent study in Cell. This study demonstrated the highest concentration of ACE2 expression is in the nose with diminishing expression in the lower respiratory tract. These findings emphasize the nasal vulnerability to COVID-19. It supports the nasal tissue as the main initial site of infection with COVID-19. Once it replicates adequately in the nasopharyngeal tissues, it can then be aspirated into the lungs. The co-senior author of the study, Dr. Richard Boucher, stated, "if the nose is the dominant initial site from which lung infections are seeded, then the widespread use of masks to protect the nasal passages, as well as any therapeutic strategies that reduce virus in the nose, such as nasal irrigation or antiviral nasal sprays, could be beneficial" [9] Such statements support the use of HSNIG.

COVID-19 has an asymptomatic prodrome phase of several days. During this time, the virus is massively replicating aggressively and is violently contagious [10]. In a recent study, it was found that the majority of asymptomatic residents in a skilled nursing facility tested positive for COVID-19. This facility was experiencing rapid and widespread transmission of COVID-19. The asymptomatic carriers appear to be significant contributors to the spread of COVID-19 in the facility. The authors conclude that focusing only on symptomatic residents to prevent the spread of COVID-19 is insufficient [11]. The accompanying editorial stated the asymptomatic transmission of COVID-19 is the "Achilles' heel" of strategies to contain the pandemic spread. Current measures are inadequate due to COVID-19 infected asymptomatic individuals being highly contagious [12] HSNIG has the potential to substantially mitigate this issue.

COVID-19 continues to replicate during the symptomatic URI stage. Shedding of the infectious virus is high during the first several days. Containment of the virus relies on isolating the patient and the use of barriers such as a face mask. Prevention of progression

to a more serious lower respiratory tract infection (LRI) relies on the immune response. During this symptomatic phase of the URI, the innate immune system is still directly involved with reducing viral replication and also stimulating the evolution of adaptive immunity [13]. Therapy such as HSNIG would enhance the innate immune response reducing the risk of spreading the virus and of developing an LRI.

DISCUSSION

The COVID-19 pandemic presents several significant issues: 1) containment 2) mitigation of progression to a life-threating condition. Social isolation, enhanced personal hygiene, and the use of environmental barriers have helped to contain the virus. However, a substantial impediment to containment remains with the highly contagious asymptomatic individuals. Advancements in therapies to reduce mortality continue to evolve, but efforts to prevent a symptomatic URI from becoming an LRI are minimal. It is conceivable that HSNIG could provide benefits for these two critical concerns with COVID-19. albeit no studies have been done on HSNIG in patients with COVID-19 evaluating replication and shedding, there is evidence with a very similar beta-coronavirus and HOCL is a known lethal agent to all microbes are showing HSNIG will reduce the replication and shedding of COVID-19 virus, there is evidence with very similar beta-coronavirus. In addition, the evidence with beta-coronavirus was in symptomatic URI individuals. It is logical to believe, HSNIG should have comparable and perhaps even more effective results in an asymptomatic infected person. Scientifically, evidence would indicate HOCL should kill COVID-19. We have recommendations to clean surfaces with bleach because it contains the antiviral substance akin to HOCL. Assuming HOCL destroys COVID-19, HSNIG performed routinely in all asymptomatic subjects regardless of infection status could substantially aid the containment of COVID-19. Empirically, it is conceivable that HSNIG would decrease the extent and gravity of COVID-19.

Definitive proof of the effectiveness of HSNIG in COVID-19 infected individuals requires randomized controlled trials.The COVID-19 pandemic is extraordinary, generating not only personal tragedies but exceptional hardships on families, communities, governments, and global relationships. Our country is utilizing bold actions socially and medically to combat this pandemic. Augmenting our current measures with a recommendation for HSNIG seems reasonable. One of our most cherished obligations as healthcare providers is to avoid harm. HSNIG is a natural, inexpensive therapy with the potential to help curtail the spread of COVID-19 and to potentially reduce the risk of progression to a life-threatening condition.

The chance of harm from this procedure is limited. Perhaps one risk is the failure to develop sufficient acquired immunity after exposure. The innate immune system, with the aid of HSNIG, might eliminate the virus before the evolution of adaptive immunity occurs. This can be evaluated once quantitative adaptive immunity tests are available. If there is no protective adaptive immunity it would be advisable to continue HSNIG until t effective vaccine. Other potential side effects he person receives an from HSNIG would include relatively minor issues such as local trauma to the nose, aspiration of saline, and ingestion of sodium chloride. Dr. Ramalingam has shown that this therapy is well accepted and tolerated. His research also demonstrated it is easy to perform and portable. This makes it amenable to be performed at work which could aid in re-opening establishments that serve the public. As stated by Dr. Gandhi and associates in the NEJM editorial, "this unprecedented pandemic calls for unprecedented measures to achieve its ultimate defeat [12]." One such measure may be HSNIG.

CONCLUSION

Additional studies are needed to confirm the benefit of HSNIG with COVID-19. Owing to the reported impact of HSNIG on the coronavirus and the safety of this intervention, the general recommendation can be delivered, It would be an inexpensive safe extension of current recommendations for social distancing and masks. It could also enhance those recommendations with a proactive measure to reduce replication and shedding of the virus. and studies can commence evaluating the wisdom of this empiric advice. If the studies show effectiveness, they can lead to fine-tuning the details of performing this therapy. With the current evidence, the hypertonic saline solution should be 3.0%. Administration of therapeutic saline irrigation and gargle should occur every eight hours. Consideration for additional application involves utilizing this therapy if symptoms are present or after possible exposure. The research will enhance these recommendations if HSNIG is proven effective in COVID-19. Withdrawal of the recommendation will occur if studies fail to show value with HSNIG in COVID-19. If studies confirm its effectiveness, HSNIG will be a safe, inexpensive, natural therapy to help stabilize the pandemic until vaccines are available.

CONTRIBUTOR STATEMENT

The authors BFB, ALD, HTH and DJV contributed equally to the writing, editing and the conceptualization of the manuscript. BFB as the corresponding senior author is responsible for the overall content as guarantor.

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COMPETING INTERESTS

The authors BFB, ALD, HTH and DJV declare NO competing interest.

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