

Local Anesthetics and Covid19 Associated Acute Respiratory Distress Syndrome: A New Therapeutic Indication?

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Abstract

The germ theory of disease does not consider the functional state of the tissue where the inflammatory response takes place. This is vastly determined by the elements that comprise the extracellular matrix and their crosstalk. Local anesthetics can modify the communication between the cells of the ECM and due to their anti-inflammatory properties mitigate inflammation without suppressing the immunity. This is especially important in the Covid19 infection where the “cytokine storm” may lead to major complications like severe acute respiratory distress syndrome and even death. Animal models provide enough support for the use of local anesthetics in case of acute lung injury and ARDS. The intravenous administration of local anesthetics [e.g. lidocaine] seems to be a practical and efficient way to control inflammation and prevent complications though clinical trials in humans are still missing. Some other uses of LA are proposed as well.

Keywords: Covid19; Extracellular matrix; Local anesthetics; Cytokine storm; Acute respiratory distress syndrome; Lung injury; Intravenous lidocaine

“The microbe is nothing, the terrain is everything.” The last words of Louis Jean Pasteur (Father of the “Germ Theory” of Disease)

“It is what we know already that often prevents us from learning” Claude Bernard (Founder of the terrain-concept).

Introduction

There is no doubt that the germ theory of disease is the currently accepted scientific theory for many diseases. The essence of this theory is that microorganisms known as pathogens or “germs” can lead to infection and disease. The term germ includes not only diverse bacterial species, but it extends to any type of microorganisms or even non-living pathogens like viruses, prions or viroids. Although this view led to the development of very important drugs against the pathogens [antibiotics, antifungal or antiviral agents], very little attention was given the functional state of the tissue where infection and the subsequent inflammation take place. The term tissue can be defined as a group of similar cells from the same origin and their extracellular matrix that carry out together a specific function. In order to understand better the inflammatory response caused by pathogen, it seems reasonable to take a closer look to the functional unit of the cell and its surroundings e.g. the Extracellular Matrix (ECM).

The Basic Regulatory System of the ECM

The cell and its environment have been traditionally seen as two separate entities in the past and it is only recently that the importance of cell to cell communication as well as the importance of the

interaction between the cellular environment (extracellular matrix) and the cell has become evident. The “terrain concept” described by Claude Bernard more than 150 years ago [1], has been the foundation of what we now define as extracellular matrix. Unfortunately, the study of the cell and its structures monopolized in a great extend the interest of the researchers. According to Bernard, the terrain has clearly protective functions and allows somatic functions to be regulated in order to maintain vital activity. Possible disturbances of these functions first cause changes in the terrain fluids [extracellular matrix], in which the cells are embedded and finally lead to dysfunction and illness. Many years later, Alfred Pischinger [2] based on the work of Bernard and many others that followed him, defined the basic regulatory system of the extracellular matrix. This system, in contrast to the specific known systems in physiology, is an unspecific system which extends everywhere in the organism. The anatomical substrate of this system is the loose connective tissue. In epithelial cell groups or in the brain where extracellular space is reduced to a minimum the extracellular matrix forms the intercellular substance. Biochemically the extracellular matrix forms a structure consisting of proteoglycans, glycosaminoglycans and structural glycoproteins playing the role of a molecular sieve through which the entire metabolism of the capillaries going to and coming from the cell must pass through. The extracellular matrix is connected into the

endocrine gland system through the capillaries, and into the central nervous system by the peripheral autonomic nerve fibers which end blindly in the extracellular matrix [3]. A very important cross communication exists between capillaries, nerves, connective tissue cells, mast cells and immune cells. Various mediators like peptides, hormones, cytokines, chemokines, neurotransmitters and many others make up the common language serving this communication between the elements of the system. At this point we should keep in mind that local anesthetics are able to modify this language by acting on cells that produce these mediators, especially in cases of inflammation [4]. Inflammation can be defined as a “host defense in response to injury of vascularized tissues” [5]. Regardless of the cause, inflammation presumably evolved as an adaptive response for restoring homeostasis. It is also generally thought that a controlled inflammatory response is beneficial (for example, in providing protection against infection), but it can become detrimental if dysregulated [6].

The basic regulatory system of the extracellular matrix is the most fundamental and oldest regulatory and information system in the organism, phylogenetically older than the hormone and nervous system [2]. It is also considered to be the place where the complex interactions between invading pathogens, host tissues and immune cells take place [7,8]. Furthermore, the ECM is a fundamental component of the host cellular microenvironment where most of the events leading to infection, disease and tissue repair take place and is also a reservoir of diverse and tissue specific signals (cytokines, growth factors, and other bioactive degradation products-matrikines) that feed into immunological pathways [9]. ECM per se can signal specific information to cells and modulate essential immune functions, such as immune cell migration into and within inflamed tissues, immune cell activation and proliferation, and cell differentiation processes, such as T cell polarization [10]. In the special case of the alveolar tissue the basic regulatory system consists of the endothelial basement membrane, the endothelial cells of the alveolar capillaries, the interstitial connective tissue with their associated fibroblasts, the alveolar epithelial basement membrane, the alveolar epithelial cells [Type I and Type II pneumocytes], and immune cells. The cross-communication between all these elements is decisive for health or disease.

Pathophysiology of Covid19-Infection

In late December 2019 groups of patients with pneumonia of unknown etiology were reported by the local health facilities in Wuhan, China. Soon after, the causative agent has been identified as a novel coronavirus by several independent laboratories in China. The causative virus has been temporarily named as 2019 novel coronavirus by the World Health Organization [11]. Since Covid19 is a new identified virus and not well studied yet, we try to extrapolate our present understanding of the pathology and pathogenesis of this virus based on our knowledge of SARS-CoV. The histopathology of SARS is characterized by Diffuse Alveolar Damage (DAD). In the initial phase the pathological alterations include necrosis of alveolar epithelial cells, intraluminal edema, fibrin exudation, hyaline membrane formation, hemorrhage and infiltrates with inflammatory cells such as monocytes or macrophages, lymphocytes and neutrophils into the alveolar wall and lumina [12-14] as well as elevated levels of serum proinflammatory cytokines and chemokines [15]. The epithelial destruction is attributed partly to the direct cytopathic effect and apoptotic mechanisms due to the viral invasion to the cells, resulting in lysis of the infected cells and inflammation of the surrounding tissue [13,16]. Therefore, the clinical deterioration of SARS-CoV infection may result from a combination of direct virus induced cytopathic effects and immunopathology induced by a “cytokine-storm” [17]. Various studies demonstrate high

serum levels of certain cytokines and chemokines during SARS-CoV infection. Kong et al. reported increased levels of circulating cytokines, such as tumor necrosis factor α , CXCL-10 [interferon gamma inducible protein 10-strong leucocyte activator], interleukin-6, and interleukin-8 [18]. Additional studies have confirmed and extended these findings concerning various proinflammatory cytokines [IL-1, IL-6, IL-12, IFN- γ , TGF- β ,] and chemokines [19-21]. Increased expression of chemokines and cytokines such as IP-10, MCP-1, IL-6 and IL-8 are important for chemotaxis and activation of neutrophils and monocytes [22]. Infiltration of these inflammatory cells corresponds with the severe pulmonary lesions observed in human cases [23-26]. This initial phase is followed by a proliferative phase with less epithelial damage, interstitial and alveolar fibrosis, bronchiolitis obliterans organizing pneumonia and regeneration that is characterized by type II pneumocyte hyperplasia [25,26]. The fibrotic phase after 14 days interstitial thickening is described with mild or moderate fibrosis and with just few inflammatory cells (mainly histiocytes and lymphocytes) [13,25,27]. Keeping in mind the pathophysiology described above, it appears reasonable that if the explosive inflammatory reaction induced by the “cytokine storm” can be confined within somehow acceptable limits for the homeostatic mechanisms of the host, it may raise the chances for survival or even complete therapy in lighter cases. Among many strategies and agents that are currently being tested, the therapeutic use of local anesthetics may offer a significant support for treatment.

Local Anesthetics and Inflammation

Local anesthetic agents are widely known and in clinical use for over a century mainly due to their nerve blocking properties. However accumulating data suggest that local anesthetics can act on non -neuronal tissues as well. It seems that local anesthetic effects on non-excitabile cells [28] like monocytes [29,30], neutrophils [31-34] and mast cells [35,36] may offer an explanation for a prolonged therapeutic effect than the pharmacological half -life of the drug [37]. Local anesthetics induce Gq-protein-complex mediated intracellular anti-inflammatory mechanisms [38], deactivate overactive granulocytes, inhibit the signaling of human NMDA receptors [39], induce vasodilatation [40] have antimicrobial properties [4], and exhibit a sympatholytic effect [41] and affect the synthesis and release of inflammatory mediators as eicosanoids, histamine, prostaglandins, and cytokines [4]. Due to the key position of the so called “cytokine storm” in the pathophysiology of SARS and Covid19 [42-48] the idea of using a drug like a local anesthetic that mitigates inflammation without suppressing the immunity seems quite reasonable. There is substantial clinical evidence supporting this idea [29,30,44-47]. Therefore, it seems worthy to consider implementing local anesthetics in the clinical practice in order to reinforce the treatment options concerning Covid19 associated pneumonia.

Local Anesthetics, Acute Lung Injury and ARDS

Acute respiratory distress syndrome is one of the most serious complications of the respiratory disease caused by Covid19 infection [48,49]. Lung vascular injury is the most important initial cause of Acute Respiratory Distress Syndrome (ARDS) [50]. Therapeutic options confine themselves to symptomatic treatment [lung-protective ventilation] rather than the cause of endothelial barrier dysfunction [51]. Local anesthetics may address the problem etiologically by effectively blocking inflammatory TNF α signaling in endothelial cells which leads to reduced neutrophil adhesion and endothelial hyperpermeability [52]. Injury to the lung endothelial barrier can occur by several mechanisms, but it seems that neutrophil-dependent

lung injury is the best-documented pathway [53-56]. In case of acute lung injury irrespective from cause, neutrophils accumulate in the lung microvasculature and become activated, leading to degranulation and the release of several toxic mediators, which result in increased vascular permeability and sustained functional loss of normal epithelial barrier. Nevertheless, neutrophils play an important role in host defense particularly against bacterial infection. Depletion of neutrophils may prevent lung injury but substantially impairs innate immunity [50]. Again, local anesthetics may offer a viable solution to the problem because neutrophils have been recognized as the primary anti-inflammatory target of local anesthetics [4,31-34]. The effects of local anesthetics on lung injury has been reported in several animal studies. Mikawa et al. examined the influence of lidocaine (2 mg/kg as bolus, then 2 mg/kg/h) on rabbits who were incubated with *E. coli* [57]. They found an increase in paO_2 by lidocaine and improved lung mechanics in terms of improved compliance and reduced resistance. There was also a reduced level of pulmonary edema in comparison to the control group. In the bronchoalveolar lavage less leukocytes and a lower albumine content were found in the lidocaine group. By the use of chemiluminescence a lower oxygen radical production could be demonstrated. Histologically there were clear changes: The formation of hemorrhages, alveolar septal thickening and the number of inflammatory cells in the alveolar space were by lidocaine visibly reduced. Similar results were obtained by Nishina et al. in acid-induced lung injury [58] and by Takao et al. in hyperoxia-related lung damage [59] on the rabbit model. An intratracheal application of hydrochloride [0.1 N, 3 ml/kg body weight] lowered the paO_2 and compliance and led to an increase of IL-6 and IL-8. Lidocaine (2 mg/kg body weight, then 2 mg/kg body weight/h) reduced superoxide anion production and counteracted morphological changes, if it was administered intravenously 10 min before or after the acid application [58]. More recent research on animal models confirmed the beneficial use of local anesthetics on lung injury [60-64].

Treatment

Unfortunately to the present day there are no clinical trials in humans for the treatment of ARDS. However, under the highly alarming conditions of Covid19 infection and its associated ARDS this problem should not discourage clinicians implementing local anesthetics to support and enhance the treatment of hospitalized patients. The valuable experience gained by the use of local anesthetics for the treatment of chronic [65,66] and postoperative pain [67-69] may pave the way to establish a protocol for the treatment of lung injury. Therefore, based on recommended lidocaine doses in the perioperative period, an administration of 0,015-0,030 mg/kg/min for 24-48h could be a starting line to establish a treatment protocol [70,71]. This is of course a general suggestion which should be adapted accordingly. Similar effects can be possibly achieved with procaine and procaine-base infusion [72] although the scientific evidence concerning procaine, lung injury and ARDS is still missing.

Conclusion

Considering the severity of the Covid19 infection with its associated complications due to the "cytokine storm" phenomenon, the therapeutic [systemic] use of local anesthetics may be justified. Taking into account the special circumstances under which hospitalized patients are being treated, systemic use of local anesthetics is more feasible and safer in comparison to local or segmental treatments that may also have the potential to alter the functional state of the lungs. Examples of local treatment may include any intervention with local anesthetics in the dermatome, myotome or sclerotome of Th2 to Th9

[sympathetic innervation of the lungs] which utilize vegetative reflexes [e.g. cutivisceral reflex path] addressing the lungs. C4 segment is also an option because it could influence the activity of the phrenic nerve and subsequently the functionality of respiration. The best example of segmental treatment is the stellate ganglion block [73-75] which could be very promising for the treatment of acute lung injury [76,77] and for attenuating the systemic inflammatory response [78].

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