Radiology and Diagnostic Imaging

Short Communication ISSN: 2515-0200

Atropine: A new perspective on prophylactic and therapeutic management of COVID-19

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Abstract

Integration of traditional knowledge and practices with new evidence can provide us the solution to intricate problems like SARS-CoV2 pandemic. Ayurveda and homeopathic systems of medicines have been using poisons like atropine successfully with meticulous processing and modulated dosages. Hence, in this period of panic, Atropine can be optimized to modulate innate immunity and limit viral replication. In the future, several new mutated viruses may come and attack us. Also, vaccine efficacy is still a major problem around the world. Hence Atropine could be considered by drug discovery efforts as the properties of Atropine for prophylactic or therapeutic choice against COVID- 19 are promising but not yet verified.

Introduction

The severe acute respiratory syndrome coronavirus (SARS COV-2) emerged at the end of 2019 which rapidly spread all over the world and the world health organization (WHO) declared COVID-19 a pandemic. In COVID-19, severity is due to the inflammation in the lung mainly at alveolar tissue and therefore several clinical trials are being conducted to control inflammations and cytokine storms in COVID-19.

The pathogen recognition receptors (PRRs) are the primary participants in the pathogenesis of cytokine release storm. The Toll-like receptor (TLRs) are the main PRRs involved in the production of pro-inflammatory cytokines and interferons. TLRs detects a broad spectrum of pathogens. TLR-7 and TLR-8 showed a significant role in coronavirus infection, however, a low level of these receptors are detected in epithelial cells [1,2]. A recent study showed that women were affected by COVID-19 less than men; maybe through sex-related differences especially through the expression of TLR-7 and TLR-8 [3]. In studies with an animal model, viral loads are mainly higher in toll-like receptor (TLR)3-/-, TIR-domain-containing adapter-inducing interferon-β (TRIF)-/-,and IL6-/- mice compared with their wild-type mice and caused severe lung inflammation [4,5]. As with the TLR-4 response to bacteria, SARSCOV-2 spike protein strongly binds with TLR-4 receptor causing extremely worsened immune response in the lung culminating in the cytokine storm, obstruct blood oxygenation resulting to multiple organ failure [6,7]. Hence TLRs may be involved in the early failure of viral load and rapid development of severe COVID-19 especially acute respiratory distress syndrome (ARDS) [8]. Coronavirus has various strategies to defeat innate immune response (IFN-1) and this inhibition leads to clinical severity [9]. The clinical examinations showed that coronavirus suppresses innate immunity during the first 10 days of infection [10-12]. The SARS COV-2 has an inadequate response of IFN -1 in vitro and animal models as compared to other respiratory RNA viruses [13,14]. Imbalance in IFN response has been associate with aging, sex difference, pre-existing medical condition, a genetic error in IFN relevant gene loci, and auto Abs [15-22]. SARS COV -2 sustains similar antagonistic mechanisms as other human coronaviruses (SARS, MERS) so it interferes with host IFN signaling by viral proteins [23,24]. In contrast investigations by Lee et.al. (2020) and Lucas et.al. (2020) discovered that patients with severe COVID- 19 had elevated levels of type 1 IFN response and pro-inflammatory response including TNF and IL-6 [25,26]. Hence the IFN system can be a double-edged weapon because it is not activated properly at the exact time.

Efficacy of interferon in COVID -19 clinical trials: The therapeutic effect of IFN treatment in COVID- 19 remains controversial [27,28]. An experimental study showed that daily rhIFN-1 α nasal drops enhanced the protection of health care workers from SARS COV-2 over 28 days without noticeable adverse results [29]. Lokungamage et.al., studied a SARS COV-2 that is sensitive to type 1 IFN pre-treatment [30]. Another study revealed that interferon response produces ACE-2 isoform mIRb-ACE-2.SARS COV-2 cannot bind to mIRb-ACE-2 because it does not contain the amino acid sequence required for SARS COV-2 attachment. Hence this data showed the benefits of IFN treatment in COVID-19 [31].

Atropine and its benefits: Inflammation is the first-line defense mechanism of various pathological conditions. This inflammation pathway is regulated by several complex factors such as cytokines, chemokines, hormones, and prostaglandins(PG). Research data have indicated that inflammatory responses can be modified by nervous and endocrine glands [32-34].

Atropine is a naturally occurring tropane alkaloid. It is chiefly found in *Atropa belladonna*, a perennial herbaceous plant from the solanaceous family. It is a sympathetic competitive antagonist of muscarinic cholinergic receptor. Atropine shows clinical and

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Received: March 02, 2021; **Accepted:** March 16, 2021; **Published:** March 19, 2021

toxic effects through an anticholinergic mechanism. Poison is the best and fast-acting medicine if it is used in very small doses. The experimental study showed that *shodhana* methods require a reduction of toxic components and these are essential to understand before use in therapeutics. Takemura et. al. showed that atropine turns off excess fluid production [35]. Hence it is highly effective at reversing bronchorrhea and bronchoconstriction [36]. The experimental study showed that atropine reduces leukocytes migration towards the site of infection by inhibition of chemotaxis and chemokines [37]. Another study revealed that the muscarinic antagonist atropine significantly reduces neutrophil influx in the lung [38]. Furthermore, intraperitoneal atropine prevents lung inflammation as effectively as intraperitoneal dexamethasone [39].

Atropine has potent antiviral activity against enveloped viruses such as HSV and Influenza regardless of the type of nucleic acid [40-42]. It acts on viral attachment to the cell and affects both innate and adaptive immune cells [37]. Belladonna 200c -a standard homeopathic medicine derived from *Atropa belladonna,* has anti-JEV activity [43,44]. A recent animal clinical study showed that Belladonna 200c increase mRNA expression of CCR-5, TLR-3, TLR-7, IFN-,α IFN-β, ISG-15, and IFIT1 but lower TLR-4 expression [45,46]. A pre-treatment study against JEV indicated that pure atropine and atropine sulfate boosting innate immunity which reduces the severity of the disease [47].

Integration of traditional knowledge and practices with new evidence can provide us the solution to intricate problems like SARS-CoV2 pandemic. Ayurveda and homeopathic systems of medicines have been using poisons like atropine successfully with meticulous processing and modulated dosages. Hence, in this period of panic, Atropine can be optimized to modulate innate immunity and limit viral replication. In the future, several new mutated viruses may come and attack us. Also, vaccine efficacy is still a major problem around the world. Hence Atropine could be considered by drug discovery efforts as the properties of Atropine for prophylactic or therapeutic choice against COVID- 19 are promising but not yet verified.

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