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Conceptual Paper

Betadine Inhalation by Nebulizer for Prevention of COVID-19-A Boon for Health Care Workers!!!

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The COVID-19 pandemic has been implicated in over 40 million cases globally with more than 1 million deaths and uncounted morbidity. As per available data Corona virus has infected more than 30% of healthcare workers (HCW) out of these infected health care professionals, more than 50% could be asymptomatic or with minimal symptomatology but could be a potential carrier of infection among the health staff and the patients and community as well. Considering this high possibility of COVID 19 infection in HCW led to increased requirements and consequent shortage of personal protective equipment (PPE) globally which further leads to the significantly increased risk to healthcare providers.

Once inhaled, virus remains in the nose and nasopharynx for few hours. The highest concentration of viral particles resides within the nasopharynx. The virus spread via respiratory droplets, fomites and possibly airborne transmission.

Frontline workers (Emergency doctors, pulmonary, IDU and ICU physicians) are involved in high-risk infectious aerosols generating procedures including, resuscitation, intubation, bronchoscopy, tracheostomy and other ICU procedures etc in COVID patients with very high viral loads and consequent risk to HCW. Hence to reduce viral exposure to health care workers are of paramount importance.

Povidone-iodine (commonly called as Betadine solution) is a broad-spectrum, non-allergenic antiseptic with activity against bacteria, fungi and viruses used since decades for surgical site cleaning and wound care Previously betadine has been found useful in both intranasal preparations against MRSA as well as oral preparations in *in-vitro* studies of SARS-CoV, MERS-CoV, H1N1 and rotavirus. Due to the known breadth of its antiviral activity and similarities in molecular structure to MERS corona virus, it can be extrapolated that PVP-I should have robust activity against corona.

Eggers., *et al*. found that at a concentration of 1% there was a reduction of viral activity of 99.99% in *in-vitro* assays. At 2 minutes, a concentration of 0.23% was enough to reduce viral loads appreciably 1. betadine is widely used as an antiseptic and is well-tolerated.

For Nebulization purpose, we are using 10% simple betadine solutions (5 Ml), which is easily available in the pharmacy and then dilute it in 50 ml to 100 ml of normal saline to make it little less irritant and around 1% or higher concentration. We are regularly using it from last 6 - 7 months, 2 or 3 times a day before goring to hospital and after coming from hospital and before sleep. The benefits of using it via nebulizer that the nebulizer runs for 7 - 10 minutes hence it gives full protection and complete protective layering of the entire tracheobronchial tree and it will go to nose, sinuses, posterior nasopharynx, oropharynx (where you can taste it as well, albeit bitter, but good antiviral activity) and then the aerosols goes through vocal cords and trachea to your lungs and deep in to the alveoli and interstitial which is the main site of attachment and attack of COVID virus, although you may taste little strange/bitter and sputum may come of the betadine colour for some time but no need to scared but it's really very useful for the health care workers and common man for prevention of infection (not like alcohol as common man believes).

Despite a frontline doctors and frequently heavily exposed to COVID patients knowingly or unknowingly with or without protection many times. I tested my own RT PCR Swab 0 times in last 6 months and always came negative, thanks to almighty GOD and betadine nebulizers. As of now, we don't know that whether betadine makes a chemical biofilms over the tracheobronchial membranes which hinders attachment of coronavirus to the cells and blocks ACE receptors (which are the attachment site of primary entry) and/or it kills or neutralizes corona virus in the same way as it does for other bacteria and viruses or what's the exact mechanism for prophylaxis but definitely in our case we can say it helps a lot and we would recommend all health care professionals to use betadine solutions 3 times a day before going to work and after coming to work and in night at a concentration of 0.5 to 1%.

Precautionary note: Although when taking nebulizer, eyes should be closed/or use eye pad so that fumes will not go to eyes or the neb mask should be tight fitting. Those pts who are allergic to any of ingredient/component of betadine MUST NOT USE IT. Pregnancy is another contraindication and uncontrolled hypothyroid/hyperthyroid patients should also avoid till they become euthyroid with the thyroxine hormones.

In kids the role is not clear but I believe that lower concentration could be used although it needs extensive testing before making any recommendation.

Now I will elaborate some research done so far on betadine and COVID virus and the results of them. although these research need further large randomised case control studies in order to prove the beneficial effects of betadine, about in my opinion being a senior doctor, no harm in taking betadine nebuliser especially by frontline workers and the lay man exposed to COVID patients and in general population so that they will not get infection or it happens it would be of less severity.

Recent research published in Infectious Disease and Therapy Journal has demonstrated BETADINE's® strong *in-vitro* virucidal activity, killing 99.99% of the SARS-CoV-2 virus in 30 seconds. The products subjected to testing were: BETADINE® antiseptic products, namely Solution (10% PVP-I), Skin Cleanser (7.5% PVP-I), Gargle and Mouthwash (1.0% PVP-I) and Throat Spray (0.45% PVP-I). "These results confirm that BETADINE® antiseptic products, used appropriately and in conjunction with other preventative treatment options including PPE, can play a role in limiting the spread of infections, including COVID-19". It also provides the medical community as well as consumers with a science-based assurance that they are using a product that is a proven defence against COVID-19 [1].

Another study conducted at Duke-NUS at the Tropical Infectious Diseases Research and Education Centre (TIDREC) at University of Malaya, Malaysia, also demonstrated strong *in-vitro* virucidal activity, with the tested product BETADINE® Gargle and Mouthwash (1.0% PVP-I) killing 99.99% of the SARS-CoV-2 virus in 15 seconds. The TIDREC research has been accepted by the British Dental Journal (BDJ) and was published as a Letter on 26 June 2020 [2]. Previously, BETADINE® antiseptic products containing povidone iodine (PVP-I) have been proven effective *in vitro* against a wide range of viruses, including coronaviruses that have caused major outbreaks such as (MERS) and SARS and also influenza H1N1 and rotavirus with good efficacy.

Researchers from various universities in Germany have carried out the first study of the effectiveness of gargling with widely-available mouthwashes on the virus. The researchers tested eight commercial products available in pharmacies against virus particles in throat-swabs taken from infected patients. To simulate real-life, the mouthwash was mixed with the virus and a substance to mimic saliva and shaken for 30 seconds. Tests revealed that all the products reduced the amount of active virus to some extent. However, three proved especially effective, reducing the amount of virus by about 99.9 per cent.

In recent *Journal of Infectious Diseases*, the researchers conclude that the findings "provide evidence that Sars-CoV-2 can be efficiently inactivated by commercially available oral rinses within short exposure times of 30 seconds". As gargling cannot stop the virus once it has invaded healthy cells, it is not a cure for anyone who has already developed Covid-19. However, it could play a role in blocking the main

route of transmission. This is believed to be via contact with aerosols and droplets produced during sneezing, coughing or talking. By attacking the virus in the mouths of both infected people and those around them, use of antiseptic gargling could be a simple and cheap additional safeguard alongside the wearing of masks and other measures such as social distancing [3].

The three are marketed in Germany under the trade names Dequonal, Iso-Betadine and Listerine Cool Mint. Their active compounds are, respectively, dequalinium chloride plus benzalkonium chloride, povidone-iodine, and ethanol plus essential oils. The tests showed that each of the three was effective even with different strains of the virus. Such measures are increasingly seen as critical to controlling the pandemic until effective vaccines become widely available. This still believed to be many months away. The researchers believe their findings justify clinical studies of the effectiveness of mouthwashes on both patients and health-care workers. Such studies are also needed to determine the best method of using the compounds, and any potential side effects.

Data suggests about a dozen studies involving various forms of mouthwashes have now been set up in hospitals in Europe, America and Asia. Results are expected over the coming months.

Another study published found that povidone-iodine demonstrates rapid *in vitro* virucidal activity against SARS-CoV-2, (COVID-19) found that All four products [antiseptic solution (PVP-I 10%), skin cleanser (PVP-I 7.5%), gargle and mouth wash (PVP-I 1%) and throat spray (PVP-I 0.45%)] achieved ≥ 99.99% virucidal activity against SARS-CoV-2, corresponding to ≥ 4 $\log_{10}$ reduction of virus titre, within 30 s of contact [1]. This study provides evidence of rapid and effective virucidal activity of PVP-I against SARS-CoV-2. PVP-I-based products are widely available for medical and personal use for hand hygiene and oral decontamination, and could be readily integrated into coronavirus disease, COVID-19, infection control measures in hospital and community settings.

Another study published in *JAMA ENT in vitro* efficacy of a betadine nasal antiseptic for rapid inactivation of SARS-CoV-2 in S Povidone-iodine nasal antiseptics at concentrations (0.5%, 1.25%, and 2.5%) completely inactivated SARS-CoV-2 within 15 seconds of contact as measured by log reduction value of greater than 3 $\log_{10}$ of the 50% cell culture infectious dose of the virus [4]. The ethanol, 70%, positive control did not completely inactivate SARS-CoV-2 after 15 seconds of contact. The nasal antiseptics tested performed better than the standard positive control routinely used for *in vitro* assessment of anti-SARS-CoV-2 agents at a contact time of 15 seconds. No cytotoxic effects on cells were observed after contact with each of the nasal antiseptics tested. They concluded that betadine nasal antiseptic solutions at concentrations as low as 0.5% rapidly inactivate SARS-CoV-2 at contact times as short as 15 seconds. Intranasal use of PVP-I has demonstrated safety at concentrations of 1.25% and below and may play an adjunctive role in mitigating viral transmission beyond PPE.

Dental practice poses a potential risk of COVID-19 cross-infection among patients, dentists and their assistants through direct exposure to saliva and indirect contact through contaminated instruments [5]. Several associations, including the Australian Dental Association, have recommended using a preprocedural mouthwash with products such as povidone iodine [6]. Authors concluded that there is direct evidence of the virucidal activity of PVP-I gargle and against SARS-CoV-2 in just 15 seconds. In today's scenario, PVP-I gargle and mouthwash could be an adjuvant to PPEs in reducing the risk of COVID-19 transmission in healthcare practices, especially when oral interventions are warranted, such as in dental practice [7].

Now Betadine inhalation solutions (Mundi Pharna. Europe) are also available, Betadine Soothing Relief Inhalation Solution is used for supportive treatment to reduce inflammation of the airways in case of bronchitis, asthma or Chronic Obstructive Pulmonary Disease (COPD). It contains Ectoin, a natural, cell-protective molecule that works with the body's natural bronchial membrane defences. Although it does not contain betadine (Povidone iodine but it could have potential role in prevention of COVID infection among the HCW. Future studies are needed for establishing the benefits of betadine inhalation solution) [8].

Conclusion

We hypothesized based on these findings that if betadine nebulizers are taken it will have antiseptic effects on the entire respiratory tract from nose to terminal bronchioles of lung and will protect us from getting coronavirus. And hence can be used as prophylaxis in Coronavirus Disease 2019 (COVID19)-negative front-line health care workers and hospital patients and contacts of the high risk of COVID positive patients. Soon we are planning to produce the results of ongoing study on the efficacy of nebulized betadine on prevention of Corona virus in frontline health care workers. Further multinational large placebo controlled trials are needed to significantly establish the role of nebuliser betadine in the prevention of corona virus especially in high risk population like frontline health care workers, elderly and those with comorbid illness with high chances of acquiring infection.

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