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The Role of Povidone Iodine Mouthwash & Nasal Spray or Drop or Inhalation for Protection (Prevention & Treatment) of Health Care Professionals as Well as Patients and Reduction of Cross Infection during Current COVID-19 Pandemic Situation

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Abstract: ***Povidone-iodine (iodine with water-soluble polymer polyvinylpyrrolidone, PVP-I) or PVP-I products for gargling the throat and spraying the nose may have a prophylatic effect during this COVID-19 outbreak. PVP-I is the proven & time trusted antiseptic agent, having best possible (99.99%) virucidal effect ((even against SARS- CoV, MERS- CoV and SARS-CoV2). (Povidone Iodine is safe for gargling as mouthwash, for inhalation or instillation as nasal spray, drop or vapour.) A protocol should be made for nasal application and oropharyngeal wash of PVP-I for the patients as well as for the health care professionals (HCP) for the prevention of disease transmission from patient to HCP or from HCP to patient. Thus the incidence of COVID-19 will be reduced. Health care professionals as well as the patient should use it prior to treat , handle or perform procedures in and around the mouth or nose regardless the patient is COVID-19 positive or not. COVID-19 positive patients should use it to reduce the viral load of aerodigestive tract. (Patients undergoing aerosol generating procedures (like suction, intubation,..) should also be treated with PVP-I.)***

1. Background

In the current COVID-19 pandemic situation, healthcare professionals are prone to be infected with SARS-CoV-2 virus more than people of any other profession (; nearly 4% of cases early in the Chinese epidemic 1 and about 12% (341 in 2850)of cases in Bangladesh are health care professionals)1.

Absentism of HCPs and spread to their family members are big threats on healthcare system at this crisis period 2. Hospitalized patients of different diseases, other than COVID-19 ,have significant risk for acquiring Corona virus infection from hospital3.

Nosocomial transmission of SARS-CoV-2 is common in ICU or Critical care unit, as Aerosol generating procedures like- ventilation, intubation, suction ,commonly performed here and the bioaersol may represent more of a potential inoculum than by community transmission 3.

Viruses often bind to receptor proteins on the surface of cells in order to entering human cells, for example, the SARS virus binds to Angiotensin Converting Enzyme 2 (ACE2) receptor.

ACE2 is considered as a host target for the treatment of coronavirus infection to block SARS-CoV-2 from entering host cells. ACE2 could be expressed in the oral cavity (and was highly enriched in epithelial cells. and lymphocytes also.) Moreover, among different oral sites, ACE2 expression was higher in tongue than buccal and gingival tissues. These findings indicate that the mucosa of oral cavity may be a potentially high risk route of 2019-nCov infection 4.

In COVID-19 high viral load is found in saliva (when the saliva of patients was analysed at the time of admission to hospital)5.

Uniquely in Japan, gargling is generally accepted and strongly recommended as a preventive measure for URTI, in addition to hand washing and the wearing of masks 6.

(In a randomized controlled trial that compared incidences of URTI between gargling and control group, it was noted a 36% decrease in the incidence of URTI with water gargling. 6)

Recent study reveals that the nasopharynx appears to have a higher viral load than that found in the oropharynx 7.

So that, nasal administration of PVP-I is as important as gargling with PVP-I mouthwash.

Aforementioned, PVP-I is the time trusted antiseptic agent, having best possible (99.99%) virucidal effect (even against SARS-CoV2).

Povidone Iodine is safe for gargling as mouthwash, for inhalation or instillation as nasal spray, drop or vapour.

PVP-I Nasal Spray directly attacks viruses by trapping and disabling them in the nasal cavity. The disabled viruses are then expelled with the product after blowing the nose 8.

By destroying/eliminating the culprit virus from it's route of entry, risk of transmission of COVID-19 from patient to health care professionals (and vice versa) will be reduced in significant amount as well as viral load of COVID-19 infected patients will be minimized.

Povidone-iodine

In 1955 Povidone-iodine (iodine with water-soluble polymer polyvinylpyrrolidone, PVP-I) was invented 9. The active moiety, non PVP-bound ('free') iodine is released into solution from the PVP-I complex. PVP itself has no microbicidal activity but rather delivers the free iodine to target cell membranes. It is this free iodine that mediates the basic mechanism of action (oxidation of amino acids and nucleic acids in biological structures), which is difficult, if not impossible, to counteract. This basic mechanism of action leads to strong microbicidal activity expressed by multiple modes of action that include the disruption of microbial metabolic pathways, as well as destabilisation of the structural components of cell membranes, causing irreversible damage to the pathogen. Consumed free iodine is then replaced by PVP-bound iodine. The concentration of free iodine is the determining factor of the microbicidal action of PVP-I. PVP-I exposure leads to destruction of cytosolic and nuclear structures in bacteria and damage to the cell wall in fungi. In a study investigating the virucidal activity of different disinfectants, electron micrographs revealed how exposure to iodine led to degeneration of the nucleoproteins of viral particles, which was the main mechanism of action 10,11 .However, disruption of surface proteins essential for the spread of enveloped viruses has also been noted 10,12. Furthermore, iodine is a scavanger of free radical oxygen species, contributing to anti inflammatory properties 10, 13. This interaction ultimately results in microbial death.

Virucidal activity

Povidone-iodine has been reported as having the highest virucidal activity profile among several antiseptics such as CHG, benzalkonium chloride (BAC), BEC and alkyldiaminoethyl-glycine hydrochloride (AEG) 10, 14. Using a standardised in vitro approach, PVP-I gargle was found to inactivate a panel of viruses that included adenovirus, mumps, rotavirus, poliovirus (types 1 and 3), coxsackie virus, rhinovirus, herpes simplex virus, rubella, measles, influenza and human immunodeficiency virus. In this study, CHG, BAC, BEC and AEG were ineffective against adenovirus, polio virus and rhinovirus but generally showed activity against the other aforementioned viruses 10, 14.

(Similarly, these formulations also showed efficacy against the severe acute respiratory syndrome coronavirus strain, with PVP-I mediating rapid inactivation of the virus (2 min of treatment). (39)

PVP-I has been shown to be active in vitro against the coronaviruses that have caused epidemics in the last two decades, namely SARS-CoV causing the severe acute respiratory syndrome (SARS) epidemic of 2002–3 and MERS-CoV the agent responsible for causing the Middle East respiratory syndrome (MERS) epidemic of 2012–13.

SARS-CoV-2 is highly homologous with SARS-CoV, and as such it is considered a close relative of SARS-CoV1015.

In his study Egger et al suggests that, upto 0.23% concentration of PVP-I is virucidal 12, 13. Kariwa showed that treatment in vitro of SARS-CoV with various preparations of PVP-I for 2 minutes was enough to reduce viral activity to undetectable levels14. The lowest concentration used was 0·23%, found in an over the counter throat spray 13. Recent studies conclude that SARS-CoV-2 should behave similarly 15.

Safety and Tolerability

After almost 60 years on the market, the safety profile of PVP-I is well-established. Although measurable systemic absorption may occur with the long-term use of PVP-I, its clinical manifestation as thyroid dysfunction is not very common. Previous studies reported PVP-I mouthwash used four times daily for a short period (2 weeks) or once-daily for a prolonged period (24 weeks) did not affect thyroid function 16, 17. However, increases in serum thyroid stimulating hormone concentrations that may occur with prolonged PVP-I treatment (24 weeks), may benefit from a 3-week drug holiday to allow the serum TSH levels to return to baseline levels 17. PVP-I is therefore not to be used in those with hyperthyroidism and other diseases of the thyroid. In addition, the use of PVP-I gargle should only be used during pregnancy and lactation if strictly indicated, and should be kept to the absolute minimum 18. PVP-I was found to be favourably tolerated by children receiving PVP-I for dental conditions 19, and in general was shown to be 20 times better tolerated than other common antiseptics 20. While a few cases of allergic dermatitis after prolonged skin contact with PVP-I have been reported 21, this is considered to be a rare complication and differs to local pruritus and skin irritation 21, 22 . Overall, the allergenic profile of PVP-I compares well to those of other antiseptics 10.

PVP-I in practice

The benefits of PVP-I are reflected in its broad-spectrum anti-infective profile, its low potential for resistance as well

as its haemostatic and anti-inflammatory properties. Furthermore, PVP-I is available in different strengths and formulations: as a 10%, 7.5% and 1% PVP-I gargle and mouthwash across Asia; and e.g. in Japan it is also available as a throat spray (0.45% w/v formulation), thereby allowing flexibility in dosing regimens to suit individual patient's needs. 10

The regimen and length of PVP-I use will depend on the condition to be treated or prevented, as well as the susceptibility of the offending micro-organisms towards PVP-I. Clearly, the desired effect, the concentration of the solution and the time of exposure need to be balanced. Patient compliance and motivation are essential, especially if longer gargling or rinsing times are necessary. In general, gargling and rinsing with 10-15 mL undiluted PVP-I followed up for a minimum of 30 s is appropriate for the treatment and prevention of sore throats 23 and for prophylactic use before, during and after surgery 24. Given the potential of PVP-I in reducing the incidence of airborne or droplet-transmitted respiratory infections (e.g. SARS, avian flu, swine flu)25,26 , undiluted PVP-I can be used as a protective measure by rinsing the mouth for 2 min up to four times a day 10.

Antiseptics, such as PVP-I, address the challenges in many clinical settings, where infectious conditions must be prevented or treated.

The topical application of iodine intranasally for the treatment of recalcitrant chronic rhinosinusitis has been described by the St. Paul's Sinus Centre team in Vancouver 27, 28. They used a 0·08% solution, which they found to be beneficial for the management of this condition, but also did not lead to any significant effect on thyroid function, mucociliary clearance or olfaction.

In a study conducted by Gluck et al. three groups received liposomal dispersion with PVP-I (2.2, 4.4 and 0% as control) in single and repeated use (3 days, three times a day) 29.

A set of functional and cytological tests as well as safety assessments were performed.

No safety-relevant finding or serious adverse events were reported, no evidence for cyto- nor genotoxicity obtained. No clinically relevant changes in mucosa appearance, nor in olfactory sense, nor in ciliary activity (sensitive indicator of local tolerance) occurred and no complaints about nasal airflow obstruction were observed. All liposomal formulations had a positive effect on the nasal mucosa, challenged by allergy in some volunteers. Application of liposomal PVP-I spray to the nasal mucosa does not result in any demonstrable limitation of the nasal function nor in detectable damage to the multilayer ciliated epithelium of the nose. Improvement of various parameters of nasal function under liposomal PVP-I suggest improved mucociliary clearance. Explanation could be humidification, improved surfactant (phospholipid) level and/or sufficient mucolytic activity of iodide due to local application of the constituents.

Another study by wutzler et al suggests that the favorable virucidal efficiency together with the preferred apoptotic route of cell death makes the liposomal PVP-I formulation a promising candidate for topical use in prevention and treatment of infections of the eye and the upper respiratory tract 30.

In normal subjects, the clearance rate of mucin layers in the oral cavity is between 1 and 8 mm per minute 31. The flow rate of saliva in hospitalized unconscious patients is very low, and clearance of PVP-I is slower than normal 32.

2. Method/ Protocol

Our proposal for the hospital setting, 1% PVP-I solution should be applied to the oral and oropharyngeal mucosa and 0.5% PVP-I solution in nasopharyngeal mucosa of patients with presumed/confirmed COVID-19 and the healthcare professional in close contact with this group.

PVP-I is virucidal (99.99%) at these concentrations, where less than 0.23% solution is suboptimal or ineffective for virucidal action. Moreover, staining of skin, mucous membranes and teeth is minimal and reversible.

Our proposal for the same application of PVP-I for a second group that includes all patients intended to have procedures (including examination) in or around the mouth and nose or aerosol generating procedures (intubation, suction, etc.) and all the healthcare professionals intended to do those procedures.

The second group should include all patients, not just those with suspected/confirmed COVID-19 infection, during the current pandemic situation (date today 9th April, 2020) of the COVID-19.

Procedures in the second group should include, ENT examination and treatment, endotracheal intubation, endoscopy and bronchoscopy, dentistry and oral surgery,

Exclusion Criteria
A history of allergy to PVP-I or its relevant excipients (alkyl phenol ether sulphate (ammonium salt), disodium hydrogen phosphate dodecahydrate), all forms of thyroid disease or current radioactive iodine treatment, lithium therapy, known pregnancy.

Medicament:
In BangladshPovidone Iodine Mouthwash 1% is commercially available (i.eViodin, Arodin). It is to be diluted with same amount of sterile water to yield a 0·5% solution for using as nasal spray or drop. Right now the nasal spray is not available in Bangladesh, though it is available in Canada and some other developed countries. If unavailable, it can be administered /instilled in nose by dropper or syringe also.

Pre-administration:
1) Benefits and risks of the proposed treatment were informed to the HCP and patients verbally. Check the exclusion criteria

2) Take the verbal consent/ written informd consent. Healthcare professionals will be offered the administration as a form of PPE (and they will record their assent on an individual form, akin to that used prior to immunisation (e.g. the 'flu jab').

Method of application:
Step 1 – for all patients/ healthcare professionals in described groups: The 0·5% PVP-I solution is administered in a dose of 0·3 ml into each nostril, preferably using an atomising device (2 sprays for average device) or if not from a syringe o dropper. The contralateral nostril is occluded and the recipient, if conscious, inhales slowly during the atomisation/ instillation. This will give a total dose of 0·33 mg of iodine.

Step 2 –For conscious patients and healthcare professionals: gargle with 10 ml of Povidone Iodine 1% mouthwash solution (undiluted) (9 ml of the 0.5% solution) for 1-2 minutes. The solution is to be distributed throughout the oral cavity and held for 30 seconds (atleast) and then gently gargled or held at the back of the throat for another 30 seconds (atleast) ,then spit out.
(It is assumed that at most 2 ml of the solution will be retained and absorbed, giving an anticipated maximum total dose of 1·1 mg of iodine.)

Step 3 – For unconscious patients: An oral care sponge swab or similar is soaked in 2-5 ml of 1% PVP-I and this is carefully wiped around all oral mucosal surfaces. Most of this solution will be retained in the mouth/ oropharynx (a small amount remaining in the sponge), giving a maximum total dose of 1·1 mg iodine.

Timing of delivery
Patients hospitalised for confirmed/ suspected COVID 19 and healthcare workers engaged in their care:

Steps 1 & 2 should be undertaken every 6 hours for patients and up to four times per day for healthcare workers (maximal frequency two hourly). For healthcare workers, it is advised that steps 1 & 2 are performed prior to contact with the patient/ patients and if repeated contact is occurring, repeated every 2–3 hours, up to 4 times a day.

Patients attending for dentistry/ oral surgery, ENT-ORL examination and treatment, endoscopy and bronchoscopy and any other action to be carried out close/ in the mouth or nose: The patient should undergo steps 1 & 2 prior to examination/ treatment. Healthcare workers conducting the procedure or in close proximity should perform steps 1 & 2 prior to contact with the patient and if multiple patients are being seen, repeat every 2–3 hours, up to 4 times a day 33.
Discussion

The role of PVP-I in common respiratory infections. Most URTIs are caused by viruses, such as adenovirus, rhinovirus, influenza, coxsackievirus, herpes simplex virus, coronavirus and respiratory simplex virus 34.

The first step in the development of URTIs is the adherence and colonisation of the respiratory pathogen to the oropharyngeal mucosa. Assuming oral entry of such pathogens, gargling offers a practical measure for their eradication 35 . Gargling has been strongly advocated for both prevention and treatment of URTIs in Japan, a practice supported by findings from studies that looked at the role of gargling in both healthy individuals and those with frequent or persistent respiratory infections 35, 36,37. In these studies, gargling with either water or PVP-I (four times daily), respectively, were found to reduce the incidence of URTIs. Furthermore, in patients experiencing chronic respiratory infections, PVP-I was found to reduce the episodes of infections with P. aeruginosa, S. aureus (including MRSA) and H. influenzae by half 35. These findings were further corroborated by a non-randomised study in which gargling with diluted PVP-I reduced the incidence of influenza-like illnesses or the common cold and subsequent absenteeism from school and the work place 38 . While the mechanism of gargling in the prevention of respiratory infections requires further investigation, an early study suggests that gargling may lead to the removal of oral/pharyngeal house dust mite protease which has been shown to increase infectivity of the influenza virus 37,39 . Gargling, intensified by the presence of PVP-I, may therefore play an important role in the prevention or reduction in the incidence of infection through droplet transmission.

Indeed, the benefit of gargling with PVP-I has been noted in Japanese clinical respiratory guidelines that recommend gargling with PVP-I (four times a day) in both inpatients and healthcare workers for the prevention of hospital-acquired pneumonia 40. PVP-I has also been recommended as a preventative measure against pandemic influenza 41,6.

Respiratory infections in the hospital setting such as aspiration pneumonia or VAP are major issues, especially in elderly people and immunocompromised patients and are associated with high rates of mortality 42, 43. Moreover, individuals with gastro-oesophageal reflux disease (10–20%) can develop recurrent or chronic aspiration pneumonia because of aspiration of gastric contents into the lungs 44 . Pneumonia is also common in patients on mechanical ventilation resulting from aspiration of salivary bacteria into the lower respiratory tract 45.

PVP-I is rapidly virucidal in vitro and its use in the manner we propose was recommended by Eggers et al for reduction of coronavirus load in the oral cavity to help prevent MERS-CoV transmission and this has not been contested 46,47,48 ,49.

There are very few contraindications to using PVP-I as a mouthwash or nasal spray. Its administration is cheap, simple and rapid using our methods.

PVP-I is readily available in healthcare worldwide. Sensitisation of PVP-I is extremely rare.

The exact duration of virucidal action of PVP-I is unknown, although thought to be at least 3 hours. The time taken for a viral particle to infect the host cell after administration on mucosa is also unknown.The risk of iodine toxicity versus the protective effect of PVP-I is taken in consideration regarding dosing regimen fo HCP & Patient. The total dose

of iodine absorbed by the suggested regimen is unknown. Upon cessation, the extrapolation of excretion data from Nelson et al, suggests that complete urinary clearance is within 5 days 50.

PVP-I nasal inhalation is a safe procedure for removing PPB (potential pathological bacteria) from the upper airway, and this method may contribute to preventing bacterial pneumonia (also) 51.

A Canadian company has launched BETADINE® COLD DEFENCE™ Nasal Spray for the early treatment of viruses, the most common cause of colds. When used at the first sign of cold symptoms, BETADINE® is proven to help reduce the length of a cold and prevent viruses from spreading and multiplying. By trapping and disabling the cold virus and reducing the number of cold viruses in the nose, BETADINE® can help defend against colds 8.

Australian company, Firebrick Pharma, has developed a nasal spray, Nasodine, that in laboratory studies, inactivated the new coronavirus, now designated SARS-CoV-2 .

The nasal spray, called Nasodine®, is not yet approved for sale in Australia. Despite this, Firebrick Pharma hopes that the new data could allow the product to be made available on a special access or limited basis for use by healthcare workers and others at risk of exposure.

The new data was provided in a report to Firebrick Pharma by a highly-regarded Australian laboratory. The tests showed that in vitro, a 60-second exposure to Nasodine reduced the amount of detectable virus by 99.97% and eliminated the infectivity of any remaining virus.

(Firebrick Pharma is quick to point out that these are laboratory data only. They also note that Nasodine is not intended as a treatment for SARS-CoV-2 infection.)

However, the company believes it could play a role as a nasal 'disinfectant' to help protect healthcare workers who are exposed to infected people. Potentially, it could also be used by infected people to reduce 'viral shedding' (release of virus from the nose), although at this stage, it has not been tested in people for either purpose.

Nasodine is a patented nasal spray containing povidone-iodine, which is a broad-spectrum anti-viral and anti-bacterial agent that has been widely used as an antiseptic and throat gargle (, but has never been developed into a nasal spray, until now.)

(Melbourne-based Firebrick Pharma claims that its formula rapidly inactivates ("kills") all known cold viruses in laboratory tests. As a re sult, the development program to date has focused on Nasodine's potential as a treatment for the common cold, and recently, the company completed human trials to establish its safety and effectiveness as a cold treatment.)

"Nasodine is unique in that it kills all respiratory viruses, and because of its non-selective mode of action, the viruses are unable to develop resistance to it. Importantly, it does not harm the delicate nasal cells while doing so. I consider it a real Australian breakthrough," said Professor Peter Friedland, the Chief Medical Officer for Firebrick Pharma. The latest coronavirus data have prompted Firebrick Pharma to speak out publicly about the product's potential beyond the common cold, in this case, the SARS-CoV-2 infection 52.

3. Conclusion

The role of PVP-I antiseptic for the maintenance of oral health, prevention and treatment of oropharyngeal infections or any upper respiratory tract infection is evidence based and unquestionnable. (though there is a discordance between the evidence base and clinical practice10.) Our recommendation: oral and nasal use of PVP-I should be started routinely throughout the Bangladesh in HCP and their patients as an adjunct to currently recommended PPE to reduce the risk of spread of COVID-19.

Contributors

All authors have equally contributed to the design of the paper, the writing of the manuscript and have seen and approved the final manuscript; they all meet the definition of an author as stated by the International Committee of Medical Journal Editors.

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