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Considerations for povidone-iodine antisepsis in pediatric nasal and pharyngeal surgery during the COVID-19 pandemic

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ABSTRACT

Purpose: Surgeons resuming elective procedures during the COVID-19 pandemic should consider strategies to mitigate risk of exposure. For otolaryngologists performing surgery on children, unique vulnerability to SARS-CoV-2 results from a regular interface with the upper respiratory tract mucosa. A growing interest in perioperative application of povidone-iodine (PVP-I) to the nasopharynx and oropharynx has emerged. The purpose of this review is to provide an evidence-based assessment of PVP-I in pediatric oral, nasal and pharyngeal surgery.

Methods: A contemporary literature review with algorithmic approach to the potential use of PVP-I in pediatric mucosal surgery.

Results: Several formulations of PVP-I have shown rapid *in vitro* virucidal activity against SARS-CoV-2. Antisepsis using 1.0% PVP-I mouthwash and 0.45% PVP-I throat spray can occur after 30 seconds of contact time. To date, *in vivo* effectiveness of PVP-I against SARS-CoV-2 has yet to be established and possible risks of its direct use on upper aerodigestive mucosa of children must be weighed.

Conclusion: Further research is required prior to strongly recommending PVP-I use in preparation for nasal, oral or pharyngeal surgery in children.

1. Introduction

The gradual return of elective surgery during the COVID-19 pandemic underscores the need for risk mitigation and safety improvement strategies. Organizations such as The Centers for Medicare & Medicaid Services (CMS) as well as The American College of Surgeons (ACS) have offered clinicians early guidance for this process [1,2]. Until an acceptable therapeutic or vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerges, surgeons must exercise caution when caring for patients with high or uncertain potential for transmission.

Pediatric otolaryngologists confront particular challenges in resuming care during this pandemic. Many of the 1.5 million ambulatory procedures performed annually on children involve the upper respiratory tract mucosa [3]. Viral load of SARS-CoV-2 is highest in the nose and pharynx in infected patients [4]. Aerosol generation or surgical manipulation of these regions carries increased risk of disease transmission to health care personnel. Algorithms for practice modification, particularly for bronchoscopic procedures, have offered practical approaches to reduce these risks [5-7]. Continued reflection and analysis of outcomes will be crucial to ensure that resumption of elective surgical procedures in pediatric otolaryngology is safe for patients, caregivers and fellow staff.

A renewed interest in the utility of povidone-iodine (polyvinylpyrrolidone iodine, PVP-I) application to the mucosal surfaces of the nose, mouth and pharynx has emerged. Solutions of iodine have been used for over 150 years as antiseptics [8] and molecular iodine in complex with the non-surfactant carrier polyvinylpyrrolidone is the most widely available iodophor used on skin and mucosa [9]. The result is an effective antimicrobial agent against a variety of viruses, fungi, protozoa, and bacteria, including anaerobic and sporulated organisms [10]. Lessening SARS-CoV-2 using PVP-I preparations is now being considered in the dental community [11] and among otolaryngologists caring for adult endonasal skull base and oncologic patients [12,13]. A similar appraisal for PVP-I as an added measure during COVID-19 has not been considered for pediatric nasal, oral and pharyngeal surgery.

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Previous literature has focused on its oral application in preventing childhood caries [14–16] and as preparation prior to oral cavity procedures [17] including pediatric cleft and craniofacial surgery [18,19]. Nonetheless, preparing the upper aerodigestive mucosal surfaces before adenoidectomy, tonsillectomy, or endonasal procedures in children may be reasonable to consider in select situations during the COVID-19 pandemic.

This review highlights the current understanding of PVP-I as it relates to its use in pediatric patients. The objective is to provide otolaryngologists with a comprehensive summary to help consider what role PVP-I may have in reducing operative risk for SARS-CoV-2 transmission. Further, a clinical algorithm and specific applicability for pediatric otolaryngology procedures is presented.

2. Discussion

2.1. Virucidal activity

The rapid antimicrobial effect of PVP-I can occur at low concentrations, but the exact mechanism of action is unknown [7]. Iodine likely attacks surface proteins of enveloped viruses and destabilizes membrane fatty acids by reacting with unsaturated carbon bonds [20]. Binding of iodine to the lipid component of enveloped viruses increases susceptibility over non-enveloped viruses [21]. The novel SARS-CoV-2 virus responsible for the COVID-19 pandemic belongs to a family of enveloped, single-stranded RNA coronaviruses [22].

The *in vivo* efficacy of PVP-I against SARS-CoV-2 is not yet proven. However, current evidence has shown that PVP-I inactivates coronaviruses, including SARS-CoV-2, *in vitro*. A similar virus was responsible for the 2003 Severe Acute Respiratory Syndrome outbreak (SARS-CoV) and the 2012 Middle East Respiratory Syndrome (MERS-CoV). Concentrations of 0.23–1% PVP-I reduced infectivity of SARS-CoV below detectable levels within 2 min [23]. Undiluted 1% PVP-I mouthwash was virucidal to MERS-CoV under both clean and dirty conditions within 15 s of application [24]. Further, when 7% PVP-I mouthwash was diluted 1:30 with water to a concentration of 0.23%, it rapidly inactivated SARS-CoV and MERS- CoV after 15 s of exposure [25]. Each of these coronaviruses have nearly identical genomes [26] to SARS-CoV-2 and both SARS coronaviruses have similar aerosol and surface stability under experimental conditions [27].

In recent months, susceptibility to PVP-I solutions has been confirmed for SARS-CoV-2. Viral titers were undetectable when incubating SARS-CoV-2 with 7.5% PVP-I at room temperature for 5 min [28]. Various formulations have also shown efficacy. After 30 s, ≥99.99% virucidal activity against SARS-CoV-2 was found for a 1% PVP-I mouthwash and a 0.45% PVP-I throat spray [29]. This body of early experimental evidence provides support that rapid application of dilute PVP-I solutions could effectively reduce viral activity of SARS-CoV-2.

The closest *in vivo* pediatric evidence assessed the impact of PVP-I on oral bacterial count and school absences for cold and influenza. Middle school-aged children had a significant reduction (99.4%) in bacterial counts immediately after gargling 0.23% PVP-I mouthwash with an increase to near baseline levels after 30 min. The children reported acceptable taste, odor, and feeling of PVP-I. Shiraishi and colleagues found that the mean absence rate from school for cold or influenza was significantly lower among children encouraged to use PVP-I mouthwash, during the 3 month period [30]. In this study, neither the frequency of daily use nor any quantitative measures on viral activity were recorded.

2.2. Common preparations

Betadine® (Aviro Health L.P., Stamford, CT) is the commonly recognized trade name for 10% PVP-I solution. This aqueous solution contains 90% water, 8.5% PVP and 1% available iodine and iodide with a free iodine concentration of 1 parts-per-million (ppm) [9]. Commercially available PVP-I preparations also include scrubs, foams, ointments along with an alcoholic solution (10% PVP-I) for quick-drying purposes and a dry powder spray (2.5% PVP-I) [9,31]. Furthermore, PVP-I is available in common strengths of 10%, 7.5% and 1% and formulations such as a gargle or mouthwash and a 0.45% throat spray depending on application [32].

Free iodine is the antimicrobial component of PVP-I solutions and is concentration-dependent. Studies suggest that the bactericidal effect follows a bell-shaped curve. As the content of free iodine increases from 1 ppm, effectiveness reaches a maximum at about 0.1% strength, or 1:100 dilution, but then decreases with further increased iodine concentration [28,33]. This reflects *in vitro* studies showing a paradoxical effect of increased antimicrobial action as the degree of dilution increases until dilutions of above 1:100, at which point the germicidal activity decreases [8]. Understanding the available formulations is important prior to use in order to avoid unnecessarily high concentrations of free iodine. Clinicians should look to avoid solutions that include alcohol for use in upper airway procedures as this could be a fuel source leading to an airway fire in the presence of electrocautery and an oxidizer [34].

2.3. Safety concerns

Fortunately, reports of adverse systemic effects following short-term use of PVP-I are rare [20]. A few local, mild reactions are worth considering. Skin exposure can cause irritant contact dermatitis and less commonly allergic contact dermatitis. This results in the recommendation to avoid PVP-I on damaged skin such as eczematous lesions of atopic dermatitis [35]. One study concluded that only 2 of the 500 patients (0.4%) had true allergic contact dermatitis from use of 1% PVP-I solution [36]. In a large, multi-center randomized trial, none of the 370 neonates receiving 10% PVP-I skin scrub prior to catheter placement developed contact dermatitis with biweekly application [37]. An anaphylactic reaction to cutaneous 10% PVP-I, though reported in children, is incredibly rare [38]. Despite its brown color, staining of teeth has not been shown in contrast to chlorhexidine gluconate, which may cause discoloration of tooth surfaces and oral mucosa in long-term usage [14,39].

Although measurable systemic absorption may occur with the long-term use of PVP-I, its clinical manifestation as thyroid dysfunction is uncommon [29]. The Wolff-Chaikoff effect describes the transient inhibitory effects of excess iodine on a mature thyroid gland [40,41]. Premature infants are particularly vulnerable to this effect and may be susceptible to thyroid inhibition from long-term excess iodine exposure [42]. A recent systematic review looked at fifteen studies describing iodine-related complications in preterm neonates for 1%–10% PVP-I solutions. The incidence of transient hypothyroidism or hyperthyrotropinaemia following exposure to topical iodine ranged from 12 to 33 per 100 infants and zero incidence in non-exposed infants. The group concluded that there is evidence that neonatal exposure to iodine-containing disinfectants causes thyroid dysfunction in infants born under 32 weeks, but larger scale studies are needed to definitively determine the nature of the relationship and impact on neurodevelopment. The authors recommended restricting exposure of iodine-containing skin disinfectants in preterm infants [43].

Within two minutes of exposure, PVP-I at concentrations of 10% and 5% have been shown to be ciliotoxic to human respiratory cells *in vitro* [44]. Lower concentrations of 2.2% or 4.4% PVP-I liposomal spray on the nasal mucosa of healthy volunteers does not result in any demonstrable limitation of nasal function or in damage to the multilayer ciliated epithelium of the nose [45]. The role for PVP-I rinses in the management of adult chronic rhinosinusitis (CRS) patients has been considered. For example, in a prospective study of 29 adult patients with recalcitrant CRS, a dilute 0.08% PVP-I sinonasal rinse as ancillary therapy improved SNOT-22 scores, without affecting thyroid function, mucociliary clearance or olfaction. Patients were instructed to rinse

each side of the nose with 0.08% PVP-I every other day for 7 weeks [46]. A similar concentration and duration of PVP-I in a retrospective review of adults with CRS reduced endoscopic signs of inflammation and patient-reported symptomatology, while minimally affecting thyroid (non-significant TSH rise after 7 weeks) and mucociliary function (nasal mucociliary clearance (NMC) time assessed by the saccharin test) [47]. It is important to remember that these concentrations have not been evaluated in children. Further, it has been found that PVP-I at concentrations greater than 0.05% can be toxic to granulocytes *in vitro* [48] while a 4% PVP-I solution is toxic to human keratinocytes [49]. Time is also an important factor for exposure. For example, an *in vitro* study found 0.5% PVP-I for up to 30 min had no toxic or detrimental effects on primary human nasal epithelial cells (HNEC) from CRS patients. However, a 30 min exposure did have a reduction in trans-epithelial electrical resistance at 60 min that persisted for 4 h [50]. All of these factors should be considered as PVP-I use, even temporarily, is weighed against potential benefits in the upper airway mucosa in children.

Finally, surgeons should recognize a risk for aspiration pneumonitis when using PVP-I solutions in the pharynx. Two reports from the pediatric craniofacial literature have described this highly morbid complication after palatoplasty surgery [17,18]. It is routine for some pediatric plastic surgeons to apply 10% PVP-I for antiseptic purposes on the face and in the mouth. Although children did recover from these events, groups have emphasized caution with this approach, including taking appropriate steps to prevent its passage into the tracheobronchial tree. This includes use of throat packs, ensuring proper endotracheal tube position, tube cuff inflation, and using dilute PVP-I solutions.

2.4. Clinical application

There are a number of scenarios in pediatric otolaryngology where the consideration of perioperative preparation with PVP-I during the COVID-19 pandemic might occur. From a procedure standpoint, any surgery involving upper aerodigestive mucosa could be included. Adenoidectomy, tonsillectomy, adenotonsillectomy, and endonasal procedures such as nasal endoscopy, endoscopic sinus surgery, and nasal cautery have the highest aerosolizing potential. Since drilling appears to carry a particularly high risk of aerosolization [51], combining PVP-I with saline irrigation in mastoid-drilling surgery could add to other protective measures such as draping and suction to potentially minimize transmissible virus from aerosolized detritus.

As the availability of testing improves, performing an elective surgery on a SARS-CoV-2 positive child may be quite uncommon. When a patient has tested negative in the hours or days prior to surgery, the added utility of PVP-I antisepsis is unclear. Nonetheless, preoperative tests can be falsely negative, related either to improper sample acquisition, low concentration of extracellular virus during early infection, or defective testing. Surgical disruption of nasal, oral or pharyngeal tissues could release even low concentrations of virus, emphasizing the particularly difficult nature of surgery in pediatric otolaryngology during this pandemic. Further, depending on community, patient, and procedural factors, there could be a role for PVP-I when testing is either unavailable, unable to be obtained, or when there is concern for a high false-negative rate. Urgent or emergent upper airway procedures such as sinonasal surgery or post-tonsillectomy hemorrhage may commence under unknown SARS-CoV-2 status. It will be up to the surgical team, anesthesia service, and operating room staff to approach these scenarios in accordance with institutional policies.

There is some evidence that PVP-I has hemostatic effects. A small pilot study of adults after anterior teeth apicoectomy found significant reductions in bleeding after applying gauze soaked with 0.5% diluted PVP-I for 1 min [52]. This benefit is of unknown significance in surgery such as adenotonsillectomy. In highly acute emergencies, such as active pharyngeal hemorrhage or acute airway embarrassment, applying PVP-I may unsafe or impossible.

Prior to the application of any PVP-I solution, clinicians must carefully read the contents of preparation. Though aqueous solutions are the most common, an alcohol-based PVP-I would have a heightened flammability risk. Given that most institutions have 10% PVP-I readily available, a 0.25% PVP-concentration could be made by diluting 6.25 mL of 10% PVP-I into 250 mL saline. Aside from using a lower concentration of PVP-I, it is also vital to take measures to decrease complications from PVP-I ingestion and aspiration. Although these severe complications have only been reported at both high doses and concentrations, it is still prudent to take precautions. Several points about performing such irrigations are crucial. First, surgeons must review the patient's previously known allergies with the parents, anesthesiologists, and nurses. Second, if the decision to use this strategy is made, a cuffed and appropriately inflated endotracheal tube must be placed. If the child is going to have PVP-I nasal irrigation, preliminary placement of oxymetazoline-soaked cotton pledgets in the nose may facilitate subsequent passage of the antiseptic solution. If feasible, the temporary placement of gauze throat packs should be applied to further reduce risk of aspiration or ingestion. Suction can additionally be placed above the throat pack or just in the hypopharynx when there is no throat pack (Fig. 1).

PVP-I can be applied to the sinonasal and oropharyngeal tissues using a large bulb syringe. One must be cautious, use slow irrigation and monitor the amount of irrigation near the throat pack protecting the endotracheal tube and esophageal inlet. A more directed application strategy would be to use gauze tonsil balls and nasal pledgets to help apply solution to the mucosa. This helps avoid copious irrigation and minimizes concern for aspiration and aerosolization. The rapid effect of this antiseptic could occur in as little as 15 s, but surgeons might consider keeping the gauze/pledgets or solution-alone in place for up to 60 s. This could be followed by gentle saline irrigation to remove excess. Once completed, it is important to suction any excess saline/PVP-I, especially if this is applied by irrigation. In patients undergoing sinus procedures, PVP-I-soaked pledgets along with irrigation may also be used during the case (Fig. 2). Furthermore, for post-tonsillectomy hemorrhage, a tonsil ball soaked in PVP-I solution could be used to put pressure on the bleeding site if time and bleeding severity allows. If this successfully tamponades or slows down the bleeding, one can prep the rest of the cavity prior to commencing with the procedure.

2.5. Areas of uncertainty

A major uncertainty is that PVP-I has not been proven to be efficacious against SARS-CoV-2 *in vivo*. Clear data on safety in pediatric mucosal application is also unknown. However, its one-time use and the minimal contact needed at the beginning of a surgical procedure is unlikely to cause significant side effects. Further studies would be required to delineate concerns related to iodine absorption.

It is also unclear what role this intervention has beyond affecting surface virus. While necessary duration of time and concentrations are relatively known, the impact upper airway procedures such as tonsillectomy have on exposing viral particles beyond the surface of the mucosa has not been studied. Some have also questioned the right method of PVP-I application. As discussed, irrigation *versus* contact with gauze or pledgets could be considered. It has been reported that the brief contact such as wound irrigation, especially if followed by a saline rinse, might minimize risk of cytotoxicity over the use of occlusive applications particularly in patients with renal insufficiency or open wounds [53]. Additional work will be important to investigate these varied strategies.

3. Conclusions

No recommendation for the use of PVP-I in preparation for pediatric nasal, oral and pharyngeal procedures can occur without further

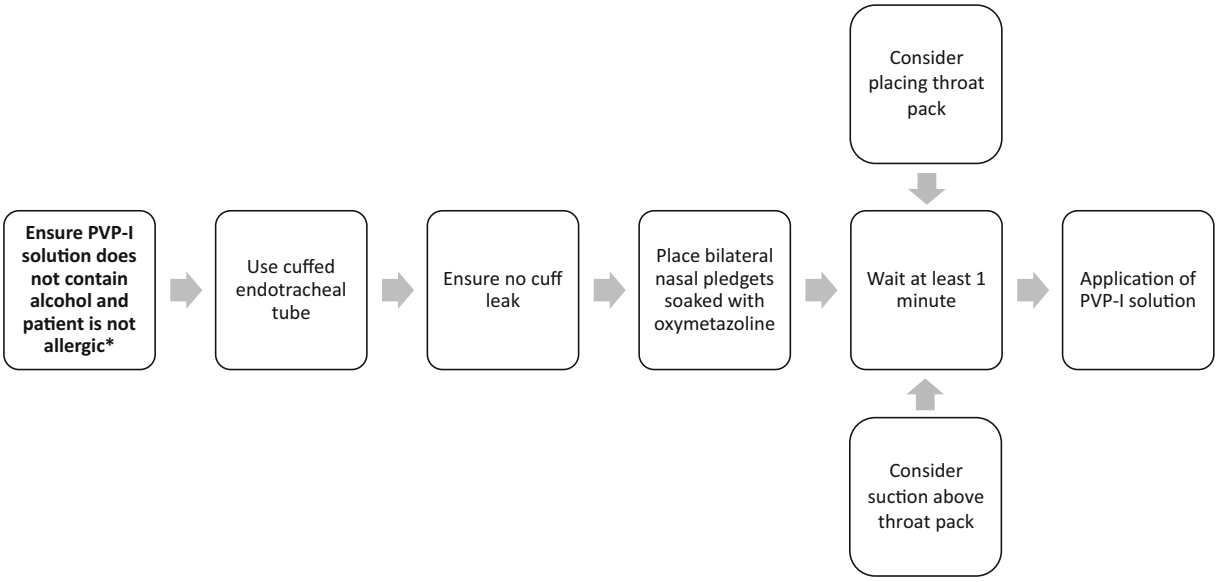

Fig. 1. Algorithmic approach to the application of PVP-I in pediatric oropharyngeal or nasopharyngeal procedures.
*Alcohol-based solutions have the risk of operating room fire. Animal and lab studies do not support fire risk with topical prepping solutions not containing alcohol.
*Ensure patient does not have an iodine allergy.

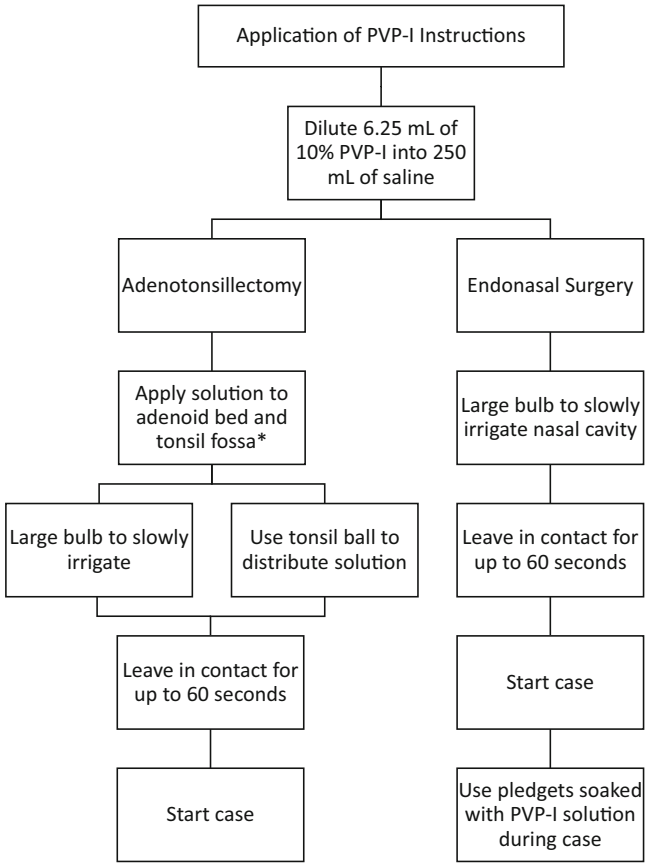

Fig. 2. Instructions for PVP-I application in pediatric otolaryngology.
*One can either slowly irrigate with a bulb suction or place the solution on a tonsil ball to coat the nasopharynx and oropharynx.
Ensure that the PVP-I irrigation is gentle and continue to monitor the throat pack and ETT to evaluate for copious solution near the airway or GI tract.

evidence. Low concentration solutions of PVP-I are effective in eliminating coronaviruses such as SARS-CoV-2 in experimental models. However, the clinical reduction in transmission is unknown. Prior studies show a largely safe side-effect profile in children, which makes PVP-I use a reasonable option to consider. Together with institutional policies and practices, surgeons must weigh the potential risks and benefits when choosing to utilize this strategy for select patients.

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Ethics approval

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Declaration of competing interest

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