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RHINOLOGY

The efficacy of diluted topical povidone-iodine rinses in the management of recalcitrant chronic rhinosinusitis: a prospective cohort study

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Abstract

Purpose Recalcitrant chronic rhinosinusitis is a persistent inflammatory condition of the sinonasal mucosa despite adequate medical therapy and sinus surgery. This study aimed to demonstrate the effectiveness and safety of dilute povidone-iodine (PVP-I) sinonasal rinses as an adjunctive therapy.

Methods Prospective cohort study. Twenty-nine recalcitrant CRS patients with endoscopic evidence of ongoing inflammation and purulent discharge were prescribed 0.08% diluted PVP-I rinses. Changes to endoscopic modified Lund–Kennedy (MLK) scores at 7 weeks post-PVP-I rinsing served as the primary outcome measure.

Results The median MLK-discharge score significantly decreased in all patients by 1.50 points post-PVP-I rinsing (p value < 0.01). The total MLK score significantly decreased in all patients by 1.50 points (p value $= 0.01$). Up to a 17% reduction in serum inflammatory markers was measured post-PVP-I rinsing. Sinonasal culture revealed a shift from moderate–heavy growth to lighter bacterial growth overall. Subjective SNOT-22 scores significantly improved overall by ≥ 1 minimal clinically important difference (MCID > 12; baseline median $= 33$; follow-up median $= 20$; p value < 0.01; $n = 22$). TSH levels increased non-significantly within normal ranges (baseline median $= 1.59$ mU/L; follow-up median $= 1.92$ mU/L; $p = 0.10$; $n = 15$). Mucociliary clearance time increased non-significantly within normal ranges (baseline median $= 9$ min; follow-up median $= 10$ min; p value $= 0.53$; $n = 17$). Olfactory Sniffin'16 scores non-significantly decreased within age-related normal ranges (baseline median $= 14$; follow-up median $= 13$; p value $= 0.72$; $n = 18$).

Conclusion A dilute 0.08% PVP-I sinonasal rinse as an ancillary therapy in recalcitrant CRS significantly reduces signs of infection alongside notable symptom improvement, without affecting thyroid function, mucociliary clearance or olfaction.

Keywords Povidone-iodine · Betadine · Chronic rhinosinusitis · Recalcitrant · Endoscopy · Treatment

Introduction

Chronic rhinosinusitis (CRS) with nasal polyposis (CRSwNP) and without nasal polyposis (CRSsNP) is an inflammatory syndrome of the sinonasal passage affecting 16% of the population, leading to notable impairment in quality of life measures [1, 2]. Approximately 25% of patients are unresponsive to appropriate medical therapy, functional endoscopic sinus surgery (FESS) and close postoperative monitoring, leading to recalcitrance [3]. Biofilms have increasingly been implicated in the pathophysiology of recalcitrant CRS mucosal inflammation [1, 4].

Biofilms are uniquely configured microbial microcolonies that exhibit evasion from host defenses and antimicrobial agents [1, 4]. CRS patients with biofilms depict increased mucous production, mucociliary dysfunction, and significant pro-inflammatory changes, factors that can contribute to disease persistence.

Limited evidence exists to support the routine use of antibiotics or antifungals in CRS management [5]. Though a vast array of alternative additive therapies has been developed, many including Manuka honey, xylitol and surfactant have demonstrated mixed results, while long-term efficacy

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and safety profiles of others have yet to be established [5]. Thereby, there is still a need for effective and safe antibiofilm therapies in recalcitrant CRS management.

Iodine, complexed to the synthetic carrier povidone (PVP-I, betadine), has been used as a general antiseptic and in wound healing for many decades [6]. PVP-I has shown to be microbicidal against a spectrum of infectious agents, including antibiotic-resistant bacteria, viruses, fungi, protozoa, as well as biofilms [6, 7]. Known to have good tolerability, rare allergenicity and a lack of resistance due to its multifaceted mechanism of action, PVP-I makes for an attractive candidate in the treatment of recalcitrant CRS [6].

Having previously obtained promising results in a retrospective analysis of PVP-I use at our centre, this prospective cohort study aimed to further validate its efficacy and safety as an adjuvant treatment in recalcitrant CRS management.

Methods

Ethical considerations

A prospective cohort study was conducted at a tertiary based rhinology centre, with Research Ethics Board approval (H17-01373). Informed consent was obtained from all included participants.

Participants

At our center, CRSsNP patients are initially treated medically with evidence-based recommendations including intranasal corticosteroids, saline irrigation and culture-directed antibiotics, along side tapered oral steroids and saline irrigations for CRSwNP patients. Patients whose symptoms persist despite appropriate medical therapy are recommended to have FESS. Post-surgically, patients continue to be managed medically primarily with oral tapered Prednisone, followed by topical Budesonide (1 mg) impregnated saline irrigation (250 mL) or topical Budesonide (0.5 mg) applied via a mucosal atomization device (MAD) to each nostril for at least 3 months.

Patients included in this study were diagnosed with recalcitrant CRSwNP, CRSsNP or with allergic fungal rhinosinusitis (AFRS), demonstrating endoscopic evidence of ongoing significant sinonasal inflammation and purulent discharge represented by an endoscopic modified Lund–Kennedy (MLK) discharge subscore of at least 1, in addition to not having attained a minimum clinically important decrease (one MCID = 8.9 points post-surgically) in their 22-item Sino-Nasal Outcome Test (SNOT-22) scores for at least 3 months despite consistent compliance to our post-operative steroid course [8–10].

Recalcitrance was defined by the failure of symptom resolution requiring an increased frequency of clinical visits along with signs of continued nasal mucosal inflammation on endoscopy despite appropriate medical therapy for at least 3 months after adequate primary or revision FESS. When considering the timeline for recalcitrance, a previous study depicted stabilization of MLK endoscopic scores and SNOT-22 scores 1 month post-operatively, with insignificant changes at the 6-month follow-up. An alternative larger scale prospective study found post-operative SNOT-22 scores changed less than one MCID starting at 3-months as the first post-operative follow-up visit, up to 5 years of follow-up [11, 12]. Patients therefore would be expected to achieve symptom resolution within 3-months for surgery. We defined our timeline for recalcitrance accordingly.

Patients were excluded if below 19 years of age, had a known history of overt thyroid dysfunction, renal disease or an autoimmune disease affecting the upper airway, diagnosed with a sinonasal tumour, immunocompromised, pregnant or breast-feeding.

Treatment

PVP-I has been investigated as a topical agent via in vitro studies to determine its ciliotoxicity at varying concentrations. Kim et al. found that more concentrated solutions of 5% and 10% PVP-I were ciliotoxic, and advised caution with its use in the nose [13]. Alternatively, as an upper limit of tolerability, PVP-I diluted to 1.25% has been shown not to be ciliotoxic in vitro, while a dilution to as low as 0.01% has shown to be the lower limit of active potency [14, 15]. At our clinic, a diluted PVP-I concentration of 0.08% was arbitrarily chosen as it was deemed to fall within the safe window of activity and permitted easy mixture for patients by diluting 2 mL of commercially available 10% aqueous Betadine into 240 mL of normal saline. Patients were instructed to rinse each side of the nose with 0.08% PVP-I every other day for 7 weeks, while continuing other concurrent treatments, namely daily topical Budesonide of 1 mg in 240 mL of saline, a separate irrigating rinse from PVP-I that all patients were already using post-operatively for at least 3 months prior to PVP-I use. Seven weeks, approximating a standard follow-up interval at our center, was chosen to provide an initial prospective safety assessment of PVP-I use in this patient population. A further larger-scale study is currently underway to further assess the long-term efficacy and safety.

Outcome measures

Changes to the validated MLK score served as the primary outcome measure. Routine rigid endoscopy was employed

to assess each nasal cavity pre-PVP-I and post-PVP-I rinsing for edema (0–2), polyps (0–2) and discharge (0–2), yielding a sum score out of 12 [16].

Additional clinical data were collected pre- and post-PVP-I rinsing as secondary outcomes inclusive of: complete blood count with differential, serum IgE, serum TSH, sinonasal culture swabs, nasal mucociliary clearance (NMC) assessed by the saccharin clearance time described by Anderson et al. and Rutland & Cole, olfactory function assessed by the validated Sniffin' 16 odour identification sticks or the University of Pennsylvania Smell Identification Test (UPSIT), and SNOT-22 scores as a validated patient-reported survey of nasal symptoms and quality of life [10, 17–20]. Olfactory function scores were all standardized to Sniffin'16 scores using conversions described by Lawton et al. [20]

Sample size and statistical analysis

Based on post-PVP-I rinsing MLK score changes shown in a retrospective study at our centre, at least 12 recalcitrant CRS patients were required to detect an improvement in MLK-discharge by one or more points, the primary outcome of this study, with a power of 80% ($p < 0.05$).

With patients serving as their own controls, primary and secondary outcome changes pre- and post-PVP-I rinsing were analyzed by the paired Wilcoxon signed-rank test. Normally distributed continuous explanatory variables were described using parametric tests, while non-parametric tests were used otherwise. Categorical explanatory variables were summarized by count. To contextualize MLK score variances amongst various candidate predictor variables including gender, diagnosis and baseline disease severity, continuous variables were transformed into categories defined by quartile ranges or medians. SNOT-22 scores were stratified by a cutoff value of 35 as a known reported predictor of patient-reported CRS symptomatology control [21]. A Fisher's extract test was employed to assess the association between the various explanatory variables and MLK-discharge score improvements. Results were considered statistically significant with p values < 0.05.

Results

Demographics

Forty-two patients were enrolled in this study, of which 29 were included in the final analysis. Seven patients had either primary or revision FESS within 1 year of commencing PVP-I rinses, while the remainder had FESS ranging from 1–16 years prior to starting PVP-I. Demographic and clinical characteristics are summarized in Table 1. Of the 13 excluded patients, six had initiated antibiotic therapy before their follow-up visit (for various, often non sinus-related complaints), four withdrew owing to PVP-I side effects, reported as headache, sinus pain, and postnasal discharge, and three were lost to follow-up.

Table 1 Patient demographic and clinical characteristics

Characteristic	Result
Mean age (SD)	63 (14)
Gender	
Male	15 (52%)
Female	14 (48%)
Median total baseline MLK score (IQR)	5 (4–7)
Diagnosis	
CRSwNP[a]	22 (76%)
CRSsNP	7 (24%)
Last sinus surgery date prior to commencing PVP-I rinses[b]	
Within 1 year	7 (24%)
Over 1 year	22 (76%)
Concurrent treatment for CRS management in addition to PVP-I and topical steroids	
None	23 (79%)
Other[c]	6 (21%)

CRSwNP chronic rhinosinusitis with nasal polyposis, *CRSsNP* chronic rhinosinusitis without nasal polyposis, *MLK* modified Lund–Kennedy

[a]CRSwNP also included either allergic fungal rhinosinusitis (AFRS; $n = 19$) or fungal ball patients ($n = 1$)

[b]Either primary or secondary functional endoscopic sinus surgery

[c]Other: treatments inclusive of montelukast or prednisone or proton pump inhibitor or nucala

Primary outcome: MLK score

A significant reduction in the MLK-discharge score was observed amongst all patients between pre- and post-PVP-I rinsing (1.50 point median decrease; 95% CI 1.00–1.50; p value < 0.01), with 62% of the cohort improving by 1 or more point, 28% remaining unchanged and 10% worsening. The percentage distribution of pre- and post-PVP-I rinsing MLK-discharge scores is represented in Fig. 1. A significant reduction in the total MLK score was also found between baseline and follow-up (1.50 point median decrease; 95% CI 3.00–0.50; p value $= 0.01$).

The percent improvement in the MLK-discharge stratified into various candidate predictor variables is illustrated in Fig. 2. Relative larger variances in MLK-discharge improvement were seen between diagnosis (27% difference) and baseline MLK-discharge score (53% difference). Further association analysis revealed a significant association (p value < 0.01) only between baseline MLK-discharge score

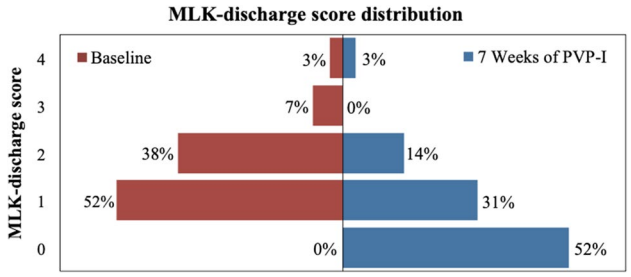

Fig. 1 Percentage distribution of MLK-discharge score at baseline and after 7-weeks of PVP-I use

and MLK-discharge improvement amongst all other candidate predictors (Table 2).

Table 2 Fisher's extract association analysis

Predictor explanatory variable	*p* value[a]
Gender	0.60
Diagnosis	0.27
Baseline total MLK	0.79
Baseline MLK-discharge	< 0.01
Baseline total WBC count	0.63
Baseline serum eosinophil count	0.28
Baseline serum IgE count	0.37
Baseline Sniffin' 16	0.44
Baseline SNOT-22	0.66
Sinonasal bacterial culture	0.34

MLK modified Lund–Kennedy, *WBC* white blood cell

[a]*p* value < 0.05 considered statistically significant

Secondary outcome: serum markers

Changes to inflammatory markers post-PVP-I rinsing are displayed in Table 3, with percent reductions ranging up to 17% in monocyte, neutrophil, IgE or eosinophil counts post-PVP-I rinsing.

Secondary outcome: sinonasal culture

The quantitative bacterial yield for the 13 culture-positive samples pre-PVP-I rinsing is mapped out in Table 4, revealing an overall shift from moderate–heavy growth to lighter pathogen growth post PVP-I rinsing. Four of 13 patients depicted no bacterial growth post-PVP-I rinsing. Pre-PVP-I treatment, species identified included *S. aureus* (38% of samples), *P. aeruginosa* (23% of samples) and *E. cloacae* (15% of samples) amongst others. The post PVP-I rinsing pattern included mainly *S. aureus* (23% of samples) and *E. coli* (15% of samples), with *S. aureus* occurring at more light or scant growths.

Secondary outcome: SNOT-22 score

Pre- and post-PVP-I rinsing SNOT-22 surveys were completed by 22 patients with scores significantly decreasing (*p* value < 0.01) from baseline (median = 33; IQR 17–46) to follow-up (median = 20; IQR 14–29). Seventy-three percent of patients demonstrated an improvement by one or more points, with 38% of these patients achieving greater than one minimal clinically important difference (MCID > 12 points for medically managed CRS) [22].

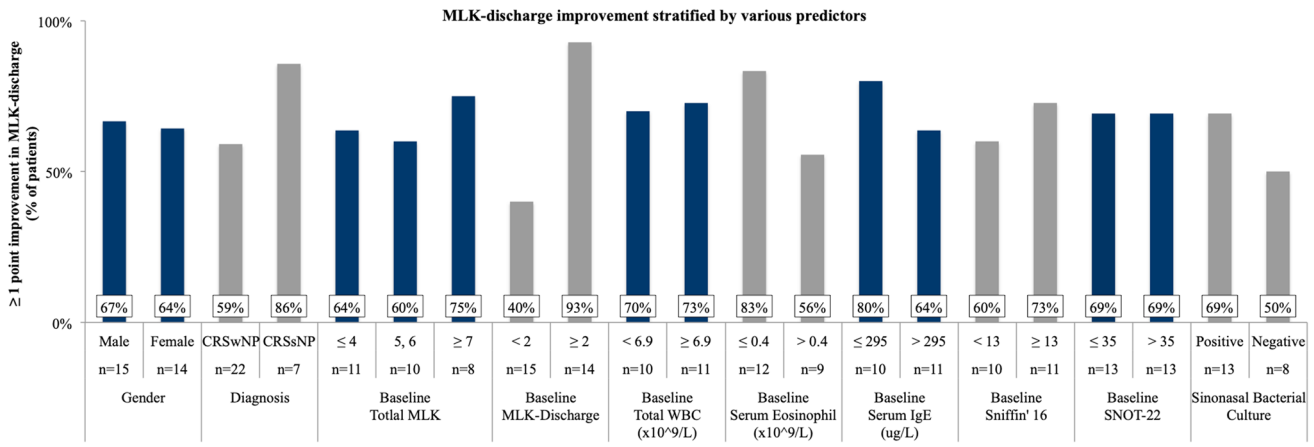

Fig. 2 MLK-discharge improvement by ≥ 1 point after 7 weeks of PVP-I use amongst patients stratified into ten predictor variables: gender, diagnosis, baseline-modified Lund–Kennedy (MLK), baseline MLK-discharge score, baseline total white blood cell (WBC) count, baseline serum eosinophil count, baseline serum IgE count, baseline Sniffin' 16 score, baseline SNOT-22 score and baseline sinonasal bacterial culture

Table 3 Serum inflammatory marker changes in patients who completed pre- and post-PVP-I rinsing blood work

Serum marker (reference range)	Count	Baseline median (IQR)	Follow-up median (IQR)	Percent reduction
Monocytes ($0.1–0.8 \times 10^9$/L)[a]	$n=15$	0.60 (0.50–0.70)	0.50 (0.50–0.70)	17
Neutrophils ($2.0–7.5 \times 10^9$/L)[b]	$n=15$	4.60 (3.95–5.20)	4.20 (3.10–4.90)	9
IgE (< 430 ug/L)[c]	$n=16$	349 (86–1108)	337 (50–1107)	3
Eosinophils ($0–0.7 \times 10^9$/L)[d]	$n=15$	0.40 (0.30–0.50)	0.40 (0.25–0.55)	0

Number of patients above the reference range

[a]Pre-PVP-I rinsing $n=2$, post-PVP-I rinsing $n=2$

[b]Pre-PVP-I rinsing $n=1$, post-PVP-I rinsing $n=0$

[c]Pre-PVP-I rinsing $n=7$, post-PVP-I rinsing $n=7$

[d]Pre-PVP-I rinsing $n=2$, post-PVP-I rinsing $n=1$

Table 4 Summary of sinonasal bacterial purulence in 13 culture-positive patients pre-PVP-I rinsing

Pre PVP-I treatment growth				Post PVP-I treatment growth				
Scant	Light	Moderate	Heavy	None	Scant	Light	Moderate	Heavy
S. pneumoniae	*K. oxytoca*	*S. aureus*	*S. aureus*	✓	*S. aureus*	*S. aureus*	*E. coli*	*E. coli*
S. aureus	*P. stutzeri*	*C. koseri*	*S. aureus*	✓	*S. maltophilia*	*S. aureus*	*M. catarrhalis*	*P. aeruginosa*
E. cloacae		*P. aeruginosa*	*S. aureus*	✓		*H. influenzae*		
		R. ornithinolytica	*P. aeruginosa*	✓		*S. liquifaciens*		
		S. maltophilia	*P. aeruginosa*					
			M. catarrhalis					
			E. cloacae					
			E. coli					

Secondary outcome: thyroid, ciliary, and olfaction safety

Amongst 15 patients with complete thyroid function tests, there was a non-significant increase (p value = 0.10) in TSH from baseline (median TSH = 1.59 mU/L; IQR 1.35–2.67) to 7 weeks post-PVP-I rinsing (median TSH = 1.92 mU/L; IQR 1.51–2.71) as shown in Fig. 3. Subclinical thyroid dysfunction was noted in two patients at baseline, though remaining such after 7 weeks of PVP-I rinsing. TSH data were further available at the 13-week mark for six patients. On one hand, four had stopped PVP-I rinsing. For three, median TSH levels decreased by 0.4 mU/L compared to levels at 7 weeks post-PVP-I rinsing. For one, the TSH level was below their baseline value. On the other hand, two had continued PVP-I rinsing. Their TSH levels were lower than at baseline.

Among the 17 patients with complete saccharin clearance, a non-significant 1-minute increase (p value = 0.53) in NMC was observed post-PVP-I rinsing, with values well within normal ranges reported as up to 30 min (Fig. 3) [17].

Given the value of 9 set as the lower limit of normosmia for a mean age group over 55 as in this study, all 18 patients with complete Sniffin'16 scores fell within normal smell identification ranges post-PVP-I rinsing as shown in Fig. 3, with a non-significant decrease in olfaction overall (p value = 0.72) [18]. A clinically significant change in Sniffin' 16 identification scores can be defined by three of more points [23]. Accordingly, a notable improvement in olfaction was observed amongst the few CRSsNP patients.

Discussion

The goal in managing CRS is to eradicate infectious components, reduce inflammation and re-establish sinus drainage with the intention of alleviating symptoms and reducing complications [8]. Yet, a number of patients continue to suffer from this disease despite repeated and appropriate medical and surgical interventions. With mounting evidence supporting the role of biofilms as an explanation for recalcitrance, we considered PVP-I as a potential adjunct for treating these patients.

Iodine is a natural element within humans, essential for the functioning of various metabolic pathways. The inactive iodophore, povidone, acts as a water-soluble carrier that permits a controlled release and thus, a sustained activity of free molecular iodine over a prolonged time period [24]. Highly effective as an antimicrobial agent in acidic pH, free

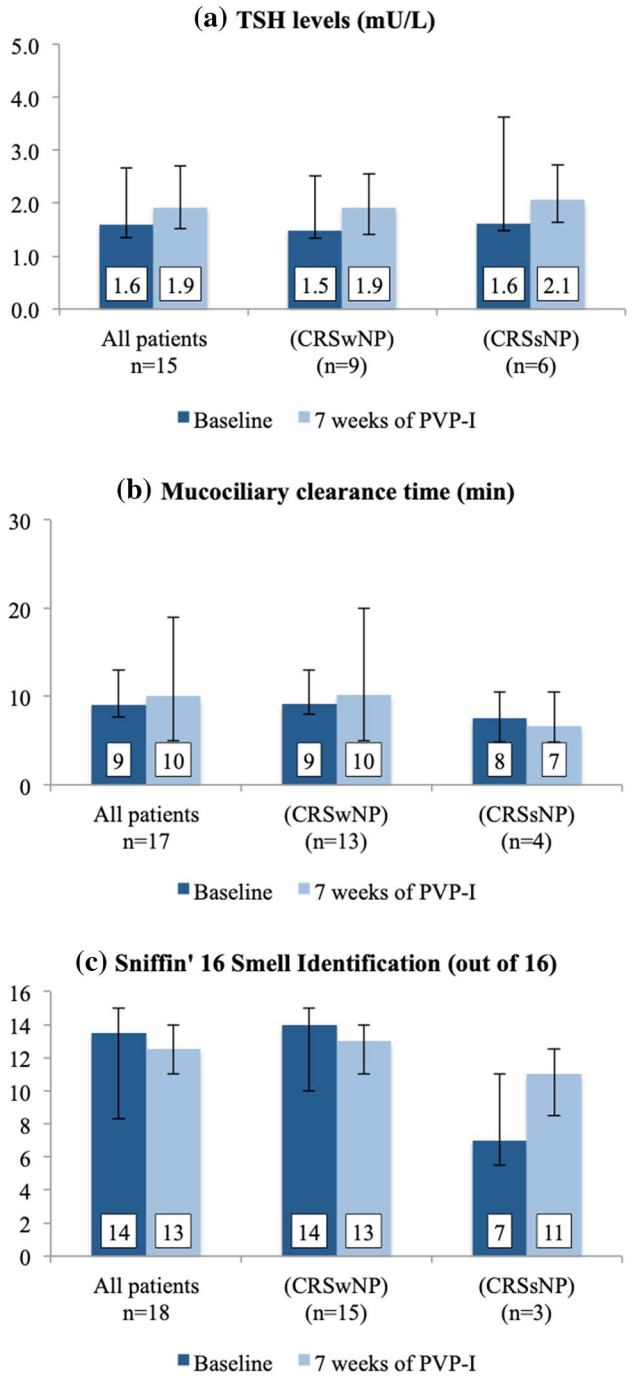

Fig. 3 Thyroid stimulating hormone (TSH), mucociliary clearance and smell identification of enrolled patients at baseline and after 7 weeks of PVP-I use, stratified by diagnosis. **a** median changes to TSH levels (p value = 0.10 in all patients). **b** Median changes to mucociliary clearance (p value = 0.53 in all patients). **c** Median changes to Sniffin' 16 smell identification (p value = 0.72 in all patients)

iodine disrupts the transport of electrons in critical cell respiration pathways and irreversibly oxidizes nucleic acids, fatty acids and amino acids causing rapid cell death, while also inhibiting the release of pathogenic virulence factors [25]. Compared to other commonly used antiseptics, PVP-I was found to have the broadest spectrum of activity against several Gram-positive and Gram-negative bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) strains, while also being effective against fungi, viruses and protozoa [25]. Due to its multimodal mechanism of action, PVP-I remains unaffected by microbial resistance as well as cross-resistance between antiseptics, despite numerous years of widespread use. In fact, PVP-I has already been considered an efficacious first-line alternative in the treatment of skin infections and has also shown to be equally effective as a 1.25% PVP-I ophthalmic solution when compared head-to-head with topical antibiotics [25, 26]. Alternatives such as PVP-I thus serve as a promising novel approach in the armamentarium of germicidal agents.

In this study, 29 patients were analyzed prospectively upon being instructed to rinse with PVP-I at least every other day, given the known prolonged release of iodine from povidone approximated to be 12–14 h. [24] At the end of 7 weeks, 62% of patients experienced a significant reduction in discharge-associated inflammation. Subjectively, the rinses provided a general sense of improvement given the amelioration in overall SNOT-22 scores by a factor of 1.1 MCID. Of note, although MLK score changes served as the primary outcome measure, a study comparing various endoscopic scoring systems to patient-reported outcome measures demonstrated that MLK scores are positively correlated to SNOT-22 subscores irrespective of surgical status, with a conclusion indicating the value of MLK use in outcomes research alongside clinical practice [12]. Moreover, a few patients did not change or depicted a worsening in endoscopic appearance. In such instances, perhaps PVP-I led to negative alterations of the mucosal microbiome or was not sufficiently effective at reducing the microbial burden as further detailed below, or that biofilm-mediated inflammation was not the predominant etiological factor.

We sought to further explore whether various objective and subjective patient factors could predict the response to PVP-I rinses, including gender, diagnoses and disease severity represented by baseline total MLK score, MLK-discharge score, total white blood cell count, serum eosinophil count, IgE count, Sniffin' 16 score, SNOT-22 score and sinonasal bacterial culture status. Unlike steroids or other alternatives that may better benefit certain CRS endotypes, PVP-I did not appear to demonstrate such predilection, nor demonstrate predictable responses by the majority of these factors, supporting our larger retrospective analysis whereby comparable benefit was obtained through a regression analysis despite diagnoses, gender and baseline total MLK score [25]. Of note however, those with a baseline MLK-discharge score of two or more did improve to a larger extent than those with

a score of one at the onset, with a notable significance on association testing. This could relate to a greater initial disease burden resulting in a more detectable objective effect. When the baseline MLK-discharge score was less than two, though only 40% of these patients improved, another 40% experienced no MLK-discharge score changes. In this case, PVP-I perhaps served as a stabilizing agent. Nonetheless, given the limited small subgroup samples preventing definite conclusions to be drawn, larger studies including regression analyses are required to better explore this trend.

Biofilm prevalence amongst CRS patients has been reported to range between 25 and 100% depending on the employed detection method [1]. While biofilms can be polymicrobial in nature, *P. aeruginosa* and *S. aureus* are the more commonly identified organisms, corroborating the sinonasal culture findings of this study, with *S. aureus* known to be more frequently associated with severe recalcitrant CRS [1, 27, 28]. In addition, *S. aureus* has been uniquely implicated in recalcitrant CRS due to its ability to evade host immunity and invade the sinonasal epithelium intracellularly thereby protecting itself from topical douches and antibiotics [4]. Nasal swab cultures as a detection method have, however. been shown to misrepresent the biofilm microbiome diversity as they merely sample the active planktonic colonies rather than the more prominent sessile community. Furthermore, co-inoculation of fungal species including *Aspergillus fumigatus*, *Bipolaris*, *Curvularis* or *Alternaria* has been documented [1, 9]. In sum, the sinonasal microbial diversity of patients in this study was restricted by the culture detection method and to bacterial growth only, limiting analysis of the results. Nevertheless, an objective shift from moderate–heavy growth to lighter pathogen growth post-PVP-I rinsing was noted. In parallel, inflammatory markers were also seen to improve including monocyte, neutrophil and IgE counts. The amelioration in these inflammatory signs likely stemmed from a reduced microbial pathogenic burden, as evidenced by sinonasal culture and MLK-discharge score reductions, in addition to PVP-I acting directly as an anti-inflammatory agent [6].

Further exploring the culture results, *S. aureus* was found more prevalent at baseline at heavier quantities, with lighter to scant growth seen at follow-up. This finding supports the known anti-*S. aureus* properties of PVP-I, which has shown to also inhibit *S. aureus* biofilms as well as methicillin-resistant *S. aureus* more effectively than other tested microbial agents even at a 0.01% dilution [29–31]. *S. aureus* is also seen to have a commensal role in the nasal passages [32]. Thus, continued growth alone may not be indicative of pathology. In one patient who had baseline heavy growth of *P. aeruginosa,* heavy growth of *P. aeruginosa* and *E. coli* was still found post-PVP-I rinsing. It is possible that a change in the nasal biodiversity permitted increased growth of more virulent organisms. Alternatively, there is also mixed evidence regarding PVP-I efficacy against *P. aeruginosa*. Though a previous study has suggested 5% PVP-I as being less effective against *P. aeruginosa* in in vitro and in rabbit models, other studies have in fact demonstrated effective *P. aeruginosa* in vitro antibiofilm activity at PVP-I concentrations of 0.07%, 3.3%, 10%, 33% and 100% [29, 33–35]. Corroboration with subsequent larger scale in vivo studies is required to confirm the efficacy of these lower PVP-I concentrations against *P. aeruginosa.* Furthermore, though *E. coli* is usually susceptible to PVP-I, recent studies have noted more virulent strains of *E. coli* taken from intra-operative biopsies of CRS patients that are related to higher pathogenicity and biofilm formation [36–38]. Due to the restricted meaning of the culture findings in this study, however, future work with more reliable genomic detection methods is required to further quantify biofilm constituents causing pathology and their responsiveness to PVP-I rinsing.

In terms of safety, thyroid dysfunction in adults is not shown to be common with PVP-I. In a 24-week prospective study, Ader et al. showed a 5% PVP-I mouth rinse increased TSH levels to a maximum of 2.5 mU/L after 6 weeks, with levels stable or slightly decreasing until 24 weeks and returning to baseline post-PVP-I cessation [39]. In this study, TSH values were also maintained within normal ranges with non-significant increases, representing minimal systemic effects. The acute changes within 7 weeks presumably represent a Wolff–Chaikoff effect, when excess iodide can transiently inhibit thyroid iodide organification, with the gland eventually escaping from this inhibitory effect with prolonged iodine exposure [40]. Further, Nobukuni et al. showed comparable changes within euthyroid limits with a 7% PVP-I gargle, while Hunt's group described no thyroid abnormalities even with 10% topical PVP-I in thermally injured patients [41].

In vitro mucociliary toxicity has been reported with 5% and 10% PVP-I [13]. Reimer's group, however, showed no significant ciliary frequency inhibition with 1.25% PVP-I in vitro, deeming it to be a well-tolerated therapeutic agent [15]. Further, normal NMC is reported as up to 30 min, beyond which impairment is considered [17]. Accordingly, the 1-minute non-significant NMC change from 9 to 10 minutes observed in the majority of patients during the 7-week rinsing period with a 0.08% solution likely represent fluctuations within normal ranges, with no evidence of ciliotoxicity.

CRS is a prominent cause of olfactory dysfunction, the severity of which is known to be higher in CRSwNP patients compared to CRSsNP [42]. In this study, CRSwNP patients experienced a clinically non-significant decrease in odor identification compared to a clinically significant improvement amongst the few CRSsNP patients, with significance defined as a three-point change in identification as per Gudziol et al. [23] To explore this tendency, further analysis revealed a median change of zero in the combined

MLK-edema and MLK-polyposis scores amongst all CRSwNP patients, implicating the presence of unresolved conductive obstruction, in contrast to a positive change to the edematous process in all CRSsNP patients. This finding suggests that a CRSsNP epithelium, void of polyps, may be more responsive to PVP-I's anti-edematous and anti-inflammatory properties at this concentration, leading to improved odorant conduction [43]. Conversely, polypoid epithelium may also suffer from eosinophilic-mediated sensorineural degenerative changes, further impairing olfaction [42]. Olfactory dysfunction may also be a product of sinus surgery, one that is not amendable to medical treatment [44]. Additional larger studies would be required to investigate whether an increased PVP-I rinsing frequency, duration or concentration, would significantly benefit olfaction in CRSwNP.

This study is the first prospective pilot clinical study to evaluate the short-term systemic effects and safety profile of very diluted PVP-I as an adjunctive sinonasal irrigating rinse, employing validated outcome measures. Using MLK-discharge score changes from a similar retrospective study conducted at our centre, this study was accordingly powered adequately to detect significant MLK-discharge score changes. Nevertheless, the study is limited by a lack of an exogenous control group, blinding of outcome assessments and full standardization of post-operative treatments, as well as small sample sizes overall. Follow-up length was also limited to one time point post-PVP-I initiation, precluding long-term assessment of PVP-I efficacy and safety. Despite these limitations, this study, in conjunction to our previous work, lends compelling insight into the value of PVP-I rinses as a microbicidal agent to sustain surgical success amongst recalcitrant CRS patients. A long-term prospective randomized controlled trial underway at our center will better delineate further recommendations, validate the safety profile of PVP-I and investigate its efficacy in reducing biofilm biomass.

Conclusion

Dilute 0.08% topical PVP-I sinonasal rinsing solution as an ancillary therapy for recalcitrant CRS significantly reduces endoscopic signs of infection, alongside a notable reduction in sinonasal bacterial growth and inflammatory markers, with a clinical and statistical significant improvement in self-reported symptoms. These changes do not appear to be limited by gender, diagnosis or baseline disease severity, though may show increased benefit to those with evidence of greater discharge at the onset of rinsing. PVP-I rinses at this concentration appear to be safe without significantly affecting thyroid function, mucociliary clearance or olfaction. Future work is required to address the limitations of this current study.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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