Topical Povidone-Iodine as an Adjunctive Treatment for Recalcitrant Chronic Rhinosinusitis

Warren Mullings*, Rikesh Panchmatia*, Katrien Samoy, Al-Rahim Habib, Andrew Thamboo, Rami Al-Salman, Amin Javer

St. Paul's Sinus Centre, Department of Surgery, University of British Columbia, Vancouver, Canada

Abstract

Objective: Recalcitrant chronic rhinosinusitis (CRS) is a persistent inflammation of the sino-nasal mucosa despite appropriate medical therapy and sinus surgery. The aim of the present study was to demonstrate the effect of topical povidone-iodine (PVP-I) sinus rinses on modified Lund–Kennedy (MLK) endoscopic scores.

Material and Methods: Retrospective chart review of patients with recalcitrant CRS (n=69) previously prescribed 0.08% adjunctive PVP-I sino-nasal rinses to evaluate changes in MLK scores and in the 22-item Sino-Nasal Outcome Test (SNOT-22) and a prospective cohort study lasting 7 weeks (n=17) were used to investigate safety outcomes.

Results: Mean total MLK decreased by 2.01 points ($p<0.05$, n=69) and median MLK-discharge decreased by 1.50 points ($p<0.05$, n=69) retrospectively. When MLK-discharge improved, 71% also had a reduction in edema. When MLK-discharge did not change, 42% had a reduction in edema. The efficacy of PVP-I on total MLK score reduction was greatest by the first follow-up visit at a median of 46 days, with sustained benefit thereafter not limited by gender, baseline disease severity, CRS subtype, duration of PVP-I use, or by concurrent antibiotic or antifungal use. Subjective SNOT-22 scores significantly improved by a minimal clinically important difference factor of 2.9 ($p=0.02$, n=15). Median thyroid-stimulating hormone (TSH) levels changed non-significantly ($p=0.1$, n=15) within normal ranges prospectively. Median mucociliary clearance time changed non-significantly ($p=0.53$, n=17) within normal ranges.

Conclusion: Ancillary 0.08% PVP-I sino-nasal rinses appear to reduce the endoscopic signs of inflammation and patient-reported symptomatology, while minimally affecting thyroid and mucociliary function. A larger scale randomized controlled trial incorporating microbiology associations is required to corroborate these findings.

Keywords: Povidone-iodine, betadine, chronic rhinosinusitis, recalcitrant, biofilm, treatment

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory condition involving the sino-nasal passage (1). Approximately 25% of patients will have ongoing chronic inflammation despite appropriate medical treatment, well-executed functional endoscopic sinus surgery (FESS), and close postoperative care, resulting in recalcitrance (2). While the pathophysiology of CRS is multifactorial in nature, mucosal biofilm-induced inflammation has been increasingly implicated in the propagation of recalcitrance (1, 3-5).

Biofilms are polymicrobial communities with unique configurations, facilitating evasion from host immune responses and a reduction in susceptibility to antimicrobial agents by as much as 1000-fold (3-5). A positive association exists between the presence of biofilms and CRS severity as evidenced by poorer post-surgical quality of life scores, repeated surgical interventions, and significant mucosal inflammatory changes, together with poor ciliary clearance, mucosal stasis, and further disease persistence (4). Accordingly, biofilm-directed therapies are important to consider in this group of patients.

Currently, insufficient evidence supports for the effectiveness of topical or oral antibiotic and antifungal therapies in recalcitrant CRS, many of which have in fact been explicitly recommended against routine use (1, 6, 7) Thereby, there is a need for safe and effective agents against a broad range of biofilm-forming organisms. In view of this, a variety of off-label topical agents, including antimicrobials, have been trialed. However, their long-term efficacy has yet to be established (6, 7).

Cite this article as:
Mullings W, Panchmatia R, Samoy K, Habib AR, Thamboo A, Al-Salman R, et al. Topical Povidone-Iodine as an Adjunctive Treatment for Recalcitrant Chronic Rhinosinusitis. Eur J Rhinol Allergy 2019; 2(2): 45-50.

*These authors are joint first authors.

Address for Correspondence: Amin Javer
E-mail: sinusdoc@me.com

Received: 22.07.2019
Accepted: 02.09.2019
DOI: 10.5152/ejra.2019.166

Iodine has been used as a general antiseptic for over 150 years. Povidone-iodine (PVP-I, polyvinylpyrrolidone-iodine, Betadine) is prepared as a soluble complex of iodine bound to povidone, a synthetic inert carrier (8). Free iodine has been shown to be microbicidal against various bacteria, fungi, and viruses, while also having an anti-inflammatory effect (8). Furthermore, resistance to PVP-I has yet to be documented owing to its broad spectrum of activity, hypersensitivity reactions are rare, and efficacy against biofilms has been demonstrated (8). As an effective antiseptic already used in various clinical domains ranging from respiratory tract infections to dermal antisepsis, the aim of the present study was to determine the value of adjunctive PVP-I sino-nasal rinses in the management of recalcitrant CRS among patients with signs of altered sino-nasal microbiome, while additionally investigating its safety through its impact on mucociliary clearance and thyroid function (9).

MATERIAL AND METHODS

Ethical Considerations

The study was approved by the Research Ethics Board for this retrospective study (H17-02237) and an ongoing prospective cohort study (H17-01373) from which thyroid function and mucociliary clearance data were obtained. Informed consent was obtained from all individual participants included in the prospective study.

Patients

Patients with CRS at a tertiary-based rhinology center are maximally treated medically with evidence-based recommendations, including intranasal corticosteroids, oral steroids, and saline irrigations, in addition to patient-tailored alternative adjuncts with more limited evidence, such as culture-directed antibiotics, antifungals (itraconazole), leukotriene modifiers, manuka honey, or surfactant, prior to FESS. Post-surgically, patients continue to be managed medically primarily with steroids, saline irrigation, and antibiotics before any other alternative therapies are introduced.

Patients included in the present study were diagnosed with recalcitrant CRS with nasal polyps (CRSwNP), CRS without nasal polyps (CRSsNP), or allergic fungal rhinosinusitis as per the Canadian guidelines or Bent and Kuhn's criteria and were required to demonstrate endoscopic evidence of ongoing sino-nasal infection at the time of PVP-I prescription (1, 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. Although modified Lund-Kennedy (MLK) endoscopic scores and 22-item Sino-Nasal Outcome Test (SNOT-22) scores have previously shown to stabilize merely 1 month postoperatively, a larger and longer prospective study found that postoperative SNOT-22 scores changed less than one minimal clinically important difference (one MCID=8.9 points) from measured postoperative follow-up visits starting at 3 months and ranging to 5 years (11-13). Our 3-month time frame in defining recalcitrance is accordingly derived as per the latter study.

Patients who were aged <19 years; had a known history of overt thyroid dysfunction, renal disease, or an autoimmune disease affecting the upper airway; diagnosed with a sino-nasal tumor; immunocompromized; and pregnant or breast-feeding were excluded from the study.

Treatment and Study Outcome

As an upper limit of tolerability, PVP-I at 1.25% has shown not to be ciliotoxic in vitro, whereas 0.01% has shown to be the lower limit of active potency (14, 15). At our clinic, a PVP-I concentration of 0.08% was arbitrarily selected as it was considered 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 at least every other day, while continuing other concurrent treatments consisting predominantly of topical budesonide–saline rinses, antibiotics, or antifungals or in some cases, montelukast, prednisone, capsaicin, manuka honey, or shampoo.

Routine rigid endoscopy was employed to assess each patients' sino-nasal cavity using the validated MLK endoscopic scoring system, grading edema (0-2), polyps (0-2), and discharge (0-2) in each nasal cavity to yield a sum score out of 12 (16). Retrospective changes in the MLK scores from baseline levels to follow-up visits served as the primary outcome measure. Clinical data was collected at regular visits, spaced approximately 6-8 weeks apart, until compliancy with PVP-I rinses subjectively decreased to <3 days/week, no follow-up data were available within 12 weeks, or an antibiotic or antifungal regimen was added or removed from the patient's management. Subjective SNOT-22 scores, a validated patient-reported survey of nasal symptoms and quality of life, were additionally collected when available if within 8 weeks of the respective clinic visit (11).

A parallel ongoing prospective cohort study with identical inclusion, exclusion, and treatment criteria was conducted to elucidate the safety of 0.08% PVP-I rinses on thyroid function and mucociliary clearance. Thyroid-stimulating hormone (TSH) data and nasal mucociliary clearance (NMC) time assessed by the saccharin test as described by Anderson et al. were collected pre- and 7 weeks post-PVP-I rinsing (17).

Statistical Analysis

All statistical analyzes were performed using RStudio version 3.4.1 (RStudio, Boston, MA, USA). Demographic and clinical characteristics were recorded for each patient. Parametric tests were used to analyze normally distributed continuous explanatory variables, whereas non-parametric tests were used otherwise. Categorical explanatory variables were summarized by count. A p-value of <0.05 was considered statistically significant.

Clinically relevant variables predicting the change in MLK scores were identified a priori upon consultation with experienced clinicians at our center, including gender, baseline disease severity, diagnosis, and time to the last follow-up visit, as well as concurrent antibiotic or antifungal use. Continuous variables were transformed into categories defined by quartile ranges to contextualize MLK score variances among each candidate predictor. A multivariate linear regression analysis was then created using previously described methods to model the independent effect of predictors with variances suspicious for significance.[18] In this analysis, diagnosis was dichotomized into CRSsNP versus CRSwNP. Given the linearity assumption was not met upon plotting the continuous variables against the change in MLK score, all candidate predictors were maintained as categories. A Chi-square test was used to assess collinearity.

RESULTS

Retrospective Objective Data: MLK Analysis

A total of 69 patients were included in this study, characteristics for whom are summarized in Table 1. Twelve patients had either primary or revision FESS within 1 year of commencing PVP-I rinses, whereas the remaining patients had any form of FESS ranging from 1 to 20 years prior to starting PVP-I.

A significant improvement was seen in the total MLK score among all patients between baseline and the last follow-up (mean decrease: 2.01 points, 95% confidence interval (CI): 1.47-2.56, paired sample t-test $p<0.05$), as well as in the MLK-discharge component specifically (median decrease: 1.50 points, 95% CI: 1.00-1.50, paired Wilcoxon signed-rank test $p<0.05$). Percent distributions of the MLK changes are shown in Table 2.

Changes to the degree of edema were evaluated in patients stratified by MLK-discharge changes, as shown in Figure 1. When the MLK-discharge score improved over the course of follow-up, an improvement of 71% was observed in the edematous process versus 42% when the MLK-discharge score did not change.

Table 1. Patient demographic and clinical characteristics of the retrospective cohort

Characteristic	Result
Mean age, years (SD)	61.2 (12.2)
Gender	
Male	36 (52%)
Female	33 (48%)
Median total baseline MLK score (IQR)	6 (5.7)
Diagnosis	
AFRS	46 (67%)
CRSsNP	16 (23%)
CRSwNP	7 (10%)
Last sinus surgery date prior to commencing PVP-I rinses[a]	
Within 1 year	12 (17%)
>1 year	57 (83%)
Concurrent treatment formulations in addition to standard topical budesonide–saline rinses	
None other	29 (42%)
Antibiotics or antifungals[b]	17 (25%)
Other[c]	13 (19%)
Antibiotic or antifungal[b]+other[c]	10 (14%)

AFRS: allergic fungal rhinosinusitis; CRSsNP: chronic rhinosinusitis without nasal polyposis; CRSwNP: chronic rhinosinusitis with nasal polyposis; IQR: interquartile range; MLK: modified Lund-Kennedy; SD: standard deviation
[a]Whether primary or secondary functional endoscopic sinus surgery
[b]Culture-directed antibiotics or itraconazole antifungal
[c]Other: treatments inclusive of montelukast or prednisone or capsaicin or manuka honey or shampoo

The percent improvement in MLK-discharge and total MLK stratified into five candidate predictor variables is illustrated in Table 3. Gender showed the largest variance of ≥30% in MLK-discharge and in total MLK percent improvement. A 30% variance in MLK-discharge improvement was also found in the total baseline MLK score category. A non-significant association was found in these variances in the univariate and multivariate regression models when adjusting for the other predictors, as outlined in Table 4.

The total MLK score was assessed at each follow-up visit of PVP-I use as shown in Figure 2. A median decrease of 2 points occurred by the first follow-up visit at a median of 46 days. Sustenance of total MLK scores at this level was observed at follow-up median times of 93 days and 151 days. Further sustenance and decrease in MLK score were observed thereafter up to 253 days of follow-up, though the smaller sample sizes hinder appreciation of this portion of the trend.

Four patients became noncompliant with PVP-I rinsing after a period of appropriate use, rinsing twice a week or less, while continuing other concurrent treatments. Comparing the total MLK scores between their last follow-up visit of adequate PVP-I rinsing to the next follow-up 6 weeks after inadequate PVP-I use, three patients worsened by ≥2 points, whereas one patient experienced no change.

Retrospective Subjective Data: SNOT-22 Analysis

Completed SNOT-22 surveys at baseline and subsequent follow-up visits were available for 15 patients. Total score significantly decreased ($p=0.02$) from baseline (median: 47, interquartile range (IQR): 32-58) to the last follow-up visit (median: 21, IQR: 15-45), which was a median of 94 days from baseline (IQR: 65-138). This corresponds to

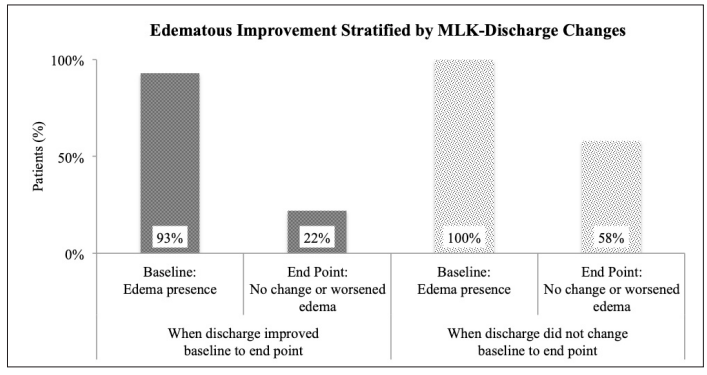

Figure 1. Edematous improvement: percentage of patients with edema (ascertained by a non-zero MLK-polyposis and/or MLK-edema score) at baseline compared to the percentage showing no change or worsening of edema (increase by 1 or more points in MLK-polyposis or MLK-edema) at the last follow-up visit, when stratified by MLK-discharge score changes

Table 2. Distributions of endoscopic changes between the last follow-up visit and baseline levels

Outcome	Overall change	Overall p-value	Improved ≥ 3 points	Improved 2 points	Improved 1 point	No change	Worsened 1 point	Worsened 2 points	Worsened ≥ 3 points
MLK-discharge	-1.50[a]	<0.05*	3%	33%	28%	28%	6%	3%	0%
MLK-total	-2.01[b]	<0.05*	39%	22%	14%	10%	10%	3%	1%

MLK: modified Lund–Kennedy endoscopic score; CI: confidence interval
[a]Median change, negative value indicating a decrease; 95% CI: 1.00-1.50
[b]Mean change, negative value indicating a decrease; 95% CI: 1.47-2.56
*Statistically significant values at $p<0.05$

a 2.9-fold overall improvement with respect to MCID (one MCID=8.9 points).

Prospective TSH and NMC Analyses

A non-significant rise in TSH was observed (p=0.1) from pre-PVP-I rinsing levels (median TSH: 1.59 mU/L, IQR: 1.35-2.67) to 7 weeks post-PVP-I rinsing levels (median TSH: 1.92 mU/L, IQR: 1.51-2.71) among 15 patients with completed thyroid function tests. TSH data were further available for six patients at the 13-week follow-up time point. Four patients had stopped PVP-I rinsing. For three patients, median TSH levels decreased by 0.4 mU/L compared with levels at 7 weeks post-PVP-I rinsing. For one patient, TSH levels had decreased to less than their baseline value. On the other hand, two patients had continued PVP-I rinsing. Their TSH levels were in fact lower than baseline values.

Median NMC time non-significantly increased (p=0.53) between baseline (9 min, IQR: 8-13 min) and 7 weeks post-PVP-I rinsing (10 min, IQR: 5-19 min) among 17 patients with completed saccharin tests.

Table 3. Percent improvement in MLK-discharge and total MLK scores stratified into five candidate predictor variables

Predictor variable	n	Total MLK Improved ≥ 1 point	MLK-discharge Improved ≥ 1 point
Gender			
Male	36	61%[a]	47%[a]
Female	33	91%[a]	82%[a]
Total baseline MLK score			
≤ 5	25	72%	72%[a]
6	25	80%	72%[a]
≥ 7	19	74%	42%[a]
Diagnoses			
AFRS	46	74%	67%
CRSsNP	16	81%	50%
CRSwNP	7	71%	71%
Days until last follow-up visit			
≤50	17	76%	65%
51-82	17	65%	65%
83-125	17	76%	82%
≥ 126	18	56%	72%
Antibiotic or antifungal use			
Yes	27	63%	70%
No	42	66%	80%

AFRS: allergic fungal rhinosinusitis; CRSsNP: chronic rhinosinusitis without nasal polyposis; CRSwNP: chronic rhinosinusitis with nasal polyposis; MLK: modified lund kennedy
[a] Variances within predictor variables suspicious for significance.

DISCUSSION

Given the empirical void of PVP-I application to the sino-nasal cavity along with the mounting evidence implicating biofilms as an important factor in recalcitrant CRS, PVP-I was considered as an ancillary therapeutic option in this population. At our clinic, patients were rinsing with PVP-I at least every other day. This was the initial dosing regimen selected by clinicians upon introducing PVP-I rinses to patients owing to the known prolonged release of iodine from povidone, approximated to be 12-14h (19). The MLK scores were compared between the last follow-up visit and baseline values, with patients serving as their own controls. In doing so, 64% of patients experienced a significant reduction in biofilm-associated inflammation as evidenced by a decrease in MLK-discharge, whereas 75% of patients demonstrated a significant overall endoscopic improvement. Additionally, while variances in MLK score improvements were noted among gender and baseline disease severity, these findings were insignificant in both the univariate and multivariate analyses. Our results suggest a trend toward comparable benefit despite gender, disease severity (baseline MLK score), CRS subtype, duration of PVP-I use, or concurrent use of antibiotics or antifungals. Furthermore, the rinses subjectively provided a general sense of improvement in a small group of patients given the significant amelioration in overall SNOT-22 scores by a factor of 2.9 MCID.

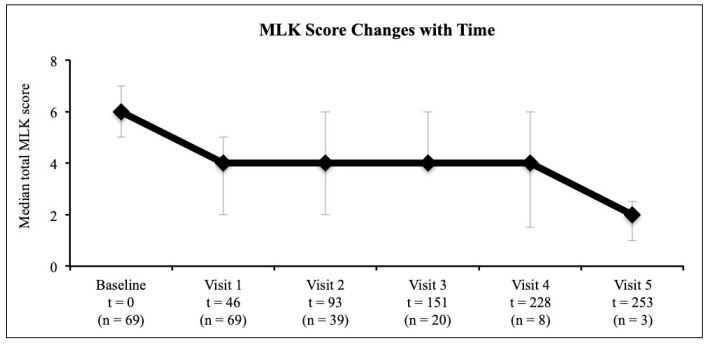

Figure 2. Median total MLK score plotted against each follow-up visit during PVP-I rinsing. Time displayed in median days from baseline. Error bars indicate interquartile ranges

Table 4. Comparison of unadjusted and adjusted linear regression estimates modeling the change in MLK-discharge score or total MLK score

Change in MLK-discharge: Suspicious predictors[a]	Univariate β (SE)	p-value	Adjusted β (SE)	p-value
Gender: Females	-0.46 (0.26)	0.09	-0.46 (0.29)	0.19
Baseline MLK ≤ 5	-0.28 (0.34)	0.42	-0.27 (0.37)	0.47
Baseline MLK 6	-0.36 (0.34)	0.30	-0.14 (0.37)	0.70
Change in total MLK: Suspicious predictors[a]	**Multivariate β (SE)**	**p-value**	**Adjusted β (SE)**	**p-value**
Gender: Females	-0.67 (0.54)	0.22	-0.70 (0.61)	0.26

[a] Candidate predictor variables included gender (males as reference), baseline MLK score (score ≥7 as reference), diagnosis, number of days to last follow-up visit and concurrent antibiotic or antifungal use

Fourteen percent of the cohort had deteriorated in their total MLK score, though predominantly by 1 point. Reasons for such findings are indeterminate and multifactorial in nature. Perhaps these patients had additional factors other than biofilm-mediated inflammation or an altered microbiome contributing to their recalcitrance that PVP-I was insufficient to address, or that PVP-I led to negative alterations in their microbiome, instead leading to a worse outcome, or that the suggested rinsing regimen was not adequately followed. Similar explanations are plausible for those who remained unchanged. Given the limits of available data in a retrospective review, further prospectively designed studies considering nasal culture samples or biofilm biomass data would be of benefit to further explore these changes. Of note, a small cohort of "non-compliant" patients worsened endoscopically upon rinsing with PVP-I only twice a week or less, despite a period of amelioration with adequate PVP-I use. This finding suggests that a regimen of rinsing at least every other day might be required to derive maximal benefit from a 0.08% PVP-I solution. Over and above, PVP-I rinses notably did not induce thyroid dysfunction or impair mucociliary clearance when monitored prospectively.

Iodine is a natural element essential for the functioning of metabolic pathways, serving also as an antimicrobial agent (8, 9). Compared with other commonly used antiseptics, such as chlorhexidine, octenidine, polyhexanide, and hexetidine, PVP-I has the broadest spectrum of activity against Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* strains, while also being effective against fungi, viruses, and protozoa (8, 9). Reduction of in vitro biofilm burden composed of MRSA, *Pseudomonas aeruginosa*, or *Candida albicans* has also been demonstrated (8, 20). Owing to its multimodal mechanism of action, PVP-I remains unaffected by microbial resistance, contrary to the growing resistance trends against antibiotics, such as mupirocin, fucidin, and gentamicin, together with antiseptics inclusive of chlorhexidine, quaternary ammonium salts, silver, and triclosan (8, 9, 21). In fact, iodine 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 (9, 22). Overall, our study lends support to the idea that PVP-I may serve as an effective microbicidal option in lieu of antibiotics and antifungals.

Moreover, PVP-I is known to counteract inflammation (8). Edema improved in 71% of our patients whose MLK-discharge improved and in 42% of patients whose MLK-discharge remained unchanged. Amelioration in inflammatory signs likely stemmed from a reduced microbial pathogenic burden, evidenced by MLK-discharge score reduction, in addition to PVP-I acting directly as an anti-edematous agent. These findings corroborate a previous dental study whereby a 0.5% PVP-I solution reduced postoperative edema compared with the control group (23). The authors hypothesized that PVP-I inhibits leukocyte chemotaxis and leukotriene B4, hence dampening the inflammatory process. PVP-I is also a scavenger of free radical oxygen species, further enhancing its anti-inflammatory properties (8).

The present study demonstrates that PVP-I rinses elicited the greatest effect after a median of 46 days, with long-term benefit thereafter. However, previous studies have depicted effective germicidal activity against planktonic, multidrug-resistant and biofilm-forming organisms between 15 s and 24 h of PVP-I exposure in vitro and in vivo with dilutions ranging from 0.01% to 10%, along with anti-edematous effects within 1 week postoperatively (8, 9, 14, 20). Intriguingly, PVP-I preparations of lower concentrations corresponded to more rapid and efficacious removal of pathogens, with 0.01% proposed as the lower limit of active potency (14). While it is likely that patients in the present study could have experienced the effects of PVP-I prior to 46 days, future work with more frequent follow-up intervals within the first few days of PVP-I use is required to characterize this effect.

With respect to safety, although 5% and 10% PVP-I solutions have shown to decrease ciliary beat frequency in vitro, no such inhibition was found with a 1.25% solution (15, 24). Further, normal NMC time has been reported up to 30 min.[17] With a 0.08% solution merely causing a 1-minute NMC fluctuation within normal ranges in the present study, PVP-I-induced ciliotoxicity is thus unlikely at such dilution. Additionally, PVP-I rinses did not induce thyroid dysfunction in the present study. In fact, the risk of thyroid dysfunction in adults is not shown to be common when PVP-I was applied at concentrations as high as 10% acutely or chronically to thermal injuries, used as a surgical irrigating rinse or employed as a gargle. Only temporal increases in serum iodine have been noticed, with TSH, T3, or T4 changes remaining within normal ranges (9, 25, 26). These reports corroborate our findings among a small prospective cohort of patients, suggesting minimal systemic absorption of iodine.

Supplementary metrics, such as olfactory tests, microbial cultures of the sinus cavities, complete blood counts, and routine patient-reported SNOT-22 measurements for all patients, were not previously part of regular visit measurements at our clinic. This information would have further elucidated the overall safety profile and efficacy of PVP-I rinses. Anecdotally, many patients had reported their sinuses feeling cleaner and more open after PVP-I irrigation, with some also reporting an improved sense of smell, subjective findings which parallel the aforementioned SNOT-22 improvements. Of note, while transient local burning or stinging has been associated with iodine, it is known to have good tolerability by large, and allergic reactions to iodine are also uncommon (9, 19, 27, 28). Although SNOT-22 scores were available for only a select few patients, a study comparing various endoscopic scoring systems to patient-reported outcome measures demonstrated that MLK scores are in fact 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 (16). Finally, the present study is limited by its retrospective design, in that the unique impact served by PVP-I rinses alone may be blurred by intrinsic biases including the lack of a control group, the confounding effects of concurrent therapies, the nonstandardization of postoperative treatments, as well as inadequate investigator blinding of MLK assessment, all of which may positively influence the results of the present study, thereby reducing the certainty of our conclusions. Nonetheless, the enrolled patients are recalcitrant in nature and have consistently failed all other evidence-based treatment options. The addition of PVP-I to their already familiar nasal rinses constituted the only change. Accordingly, despite the limitations of the present study, the outcomes could still be attributed due to the known effects of PVP-I, lending preliminary insight into the potential value of PVP-I rinses as a safe microbicidal agent to sustain objective and subjective surgical success among patients with recalcitrant CRS. Larger scale prospective and randomized controlled studies to address limitations of the current study design are indicated to validate these findings.

CONCLUSION

To the best of our knowledge, this is the first clinical study exploring topical PVP-I sino-nasal rinses in the management of recalcitrant CRS. A 0.08% rinsing solution significantly reduced endoscopic signs of infection and

edema, benefits not limited by gender, diagnosis, or disease severity. The rinses lend an overall sense of subjective wellbeing, may permit long-term benefit with sustained use, and depict a trend toward equal effectiveness with or without concomitant antibiotic or antifungal therapy. Thyroid dysfunction or ciliotoxicity is not evident by the rinses at this concentration. While PVP-I may serve as a promising novel approach in the armamentarium of germicidal agents against CRS postoperatively to sustain surgical success, a prospective randomized controlled trial underway at our center will better delineate further recommendations, validate its safety profile, and investigate its efficacy in reducing biofilm biomass.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of University of British Columbia – Providence Health Care Research Ethics Board (H17-02237/2017),

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Acknowledgements: The authors acknowledge Sara Derikvand and Jennifer Payandeh for assistance with ethics application as well as the conduct of the study.

Author Contributions: Concept - W.M., A.J., AT.; Design - W.M., R.P., A.T., A.J.; Supervision - A.J., A.T.; Fundings - A.T., A.J.; Materials - A.T., A.J.; Data Collection and/or Processing - W.M., R.P., K.S., R.A., A.H.; Analysis and/or Interpretation - A.H., A.J., A.T., R.A., K.S.; Literature Search - R.P., W.M., A.J., A.T., R.A., K.S.; Writing Manuscript - R.P.; Critical Review - W.M., A.H., A.T., A.J., K.S., R.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Desrosiers M, Evans GA, Keith PK, Wright ED, Kaplan A, Bouchard J, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. Allergy Asthma Clin Immunol 2011; 7: 1-38. [CrossRef]
2. Rudmik L, Soler ZM, Hopkins C, Schlosser RJ, Peters A, White AA, et al. Defining appropriateness criteria for endoscopic sinus surgery during management of uncomplicated adult chronic rhinosinusitis: a RAND/UCLA appropriateness study. Int Forum Allergy Rhinol 2016; 6: 557-67. [CrossRef]
3. Cohen M, Kofonow J, Nayak JV, Palmer JN, Chiu AG, Leid JG, et al. Biofilms in chronic rhinosinusitis: A review. Am J Rhinol Allergy 2009; 23: 255-60. [CrossRef]
4. Foreman A, Jervis-Bardy J, Wormald PJ. Do biofilms contribute to the initiation and recalcitrance of chronic rhinosinusitis? Laryngoscope 2011; 121: 1085-91. [CrossRef]
5. Ramakrishnan Y, Shields RC, ElBadawey MR, Wilson JA. Biofilms in chronic rhinosinusitis: What is new and where next? J Laryngol Otol 2015; 129: 744-51. [CrossRef]
6. Rudmik L, Hoy M, Schlosser RJ, Harvey RJ, Welch KC, Lund V, et al. Topical therapies in the management of chronic rhinosinusitis: An evidence-based review with recommendations. Int Forum Allergy Rhinol 2013; 3: 281-98. [CrossRef]
7. Varshney R, Lee JT. Current trends in topical therapies for chronic rhinosinusitis: update and literature review. Expert Opin Drug Deliv 2017; 14: 257-71. [CrossRef]
8. Bigliardi PL, Alsagoff SAL, El-Kafrawi HY, Pyon JK, Wa CTC, Villa MA. Povidone iodine in wound healing: A review of current concepts and practices. Int J Surg 2017; 44: 260-8. [CrossRef]
9. Kanagalingam J, Feliciano R, Hah JH, Labib H, Le TA, Lin JC. Practical use of povidone-iodine antiseptic in the maintenance of oral health and in the prevention and treatment of common oropharyngeal infections. Int J Clin Pract 2015; 69: 1247-56. [CrossRef]
10. Gan EC, Javer AR. Fungal Rhinosinusitis. In: Watkinson JC, Clarke RW, eds. Scott-Brown's Otorhinolaryngology and Head and Neck Surgery. 8th ed. London: Hodder Arnold, 2018. [CrossRef]
11. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol 2009; 34: 447-54.[CrossRef]
12. Hopkins C, Slack R, Lund V, Brown P, Copley L, Browne J. Long-term outcomes from the english national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Laryngoscope 2009; 119: 2459-65. [CrossRef]
13. Lind H, Joergensen G, Lange B, Svendstrup F, Kjeldsen AD. Efficacy of ESS in chronic rhinosinusitis with and without nasal polyposis: a Danish cohort study. Eur Arch Otorhinolaryngol 2016; 273: 911-9. [CrossRef]
14. Berkelman Rl, Holland Bw, Anderson Rl. Increased Bactericidal Activity of Dilute Preparations of Povidone-Jodine Solutions. J Clin Microbiol 1982; 15: 5.
15. Reimer K, Wichelhaus TA, Schäfer V, Rudolph P, Kramer A, Wutzler P, et al. Antimicrobial Effectiveness of Povidone-Iodine and Consequences for New Application Areas. Dermatology. 2002; 204: 114-20. [CrossRef]
16. Psaltis AJ, Li G, Vaezeafshar R, Cho KS, Hwang PH. Modification of the Lund-Kennedy endoscopic scoring system improves its reliability and correlation with patient-reported outcome measures. Laryngoscope 2014; 124: 2216-23. [CrossRef]
17. Deborah S, Km P. Clinical Research in Pulmonology Measurement of Nasal Mucociliary Clearance. Clin Res Pulmonol 2014; 2: 2-5.
18. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? BMJ 2009; 338: 1317-20. [CrossRef]
19. Casado AF, Lachapelle J-M, Tennstedt D, Lambert J, Leroy B, Micali G, et al. Antiseptics in the era of bacterial resistance: a focus on povidone iodine. Clin Pract 2013; 10: 579-92. [CrossRef]
20. Hoekstra MJ, Westgate SJ, Mueller S. Povidone-iodine ointment demonstrates in vitro efficacy against biofilm formation. Int Wound J 2017; 14: 172-9. [CrossRef]
21. Percival SL, Finnegan S, Donelli G, Vuotto C, Rimmer S, Lipsky BA. Antiseptics for treating infected wounds: Efficacy on biofilms and effect of pH. Crit Rev Microbiol 2016; 42: 293-309.
22. Isenberg SJ, Apt L, Valenton M, Sharma S, Gard P, Thomas PA, et al. Prospective, Randomized Clinical Trial of Povidone-Iodine 1.25% Solution Versus Topical Antibiotics for Treatment of Bacterial Keratitis. Am J Ophthalmol 2017; 176: 244-53. [CrossRef]
23. Arakeri G, Brennan PA. Povidone-iodine: an anti-oedematous agent? Int J Oral Maxillofac Surg 2011; 40: 173-6. [CrossRef]
24. Kim JH, Rimmer J, Mrad N, Ahmadzada S, Harvey RJ. Betadine has a ciliotoxic effect on ciliated human respiratory cells. J Laryngol Otol 2015; 129: 45-50. [CrossRef]
25. Sibbald R, Leaper D, Queen D. Iodine made easy. Wounds Int 2011; 2:1-6.
26. Tan NC, Foreman A, Jardeleza C, Douglas R, Vreugde S, Wormald PJ. Intracellular Staphylococcus aureus: The Trojan horse of recalcitrant chronic rhinosinusitis? Int Forum Allergy Rhinol 2013; 3: 261-6. [CrossRef]
27. Lachapelle JM. A comparison of the irritant and allergenic properties of antiseptics. Eur J Dermatol 2014; 24: 3-9.[CrossRef]
28. Woo KY. Management of non-healable or maintenance wounds with topical povidone iodine. Int Wound J 2014; 11: 622-6.[CrossRef]