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Povidone iodine (Betadine) spray for upper respiratory tract infections: Two pilots randomized controlled studies

Povidone iodine spray for URTI

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Abstract: Povidone-iodine (PVPI) sprays may benefit patients with upper respiratory tract inflammations (URTI). This study evaluated the efficacy of PVPI nasal and throat sprays in patients with URTI and their effect on bacterial and viral loads. Two double-blind pilot studies enrolled 10 patients each with rhinitis and pharyngitis/tonsilitis, respectively. In the nasal spray (NS) study, the test spray was PVPI (0.5% w/v) and in the throat spray (TS) study, it was PVPI (0.45% w/v). In addition to standard therapy, patients randomly received either test (n=5) or placebo (n=5) by self-administration as 2–3 sprays, 3 times daily. Evaluations included changes in the total nasal symptoms score (TNSS) in the NS study, in pharyngitis/tonsilitis symptoms on a 5-point Likert scale in the TS study, and in bacterial and viral loads in both studies. By Day 5, in the NS study, the PVPI group showed a greater reduction in TNSS from baseline (97.30% versus 84.21% in placebo) and the virus was detected in fewer patients (1 versus 3 at baseline). In the TS study, by Day 5, in the PVPI group, the mean Likert score of pharyngitis/tonsilitis symptoms had reduced more (93.75% versus 85.71% in the placebo group) and the virus was detected in fewer patients (none versus 4 at baseline). In both studies, normal bacterial flora growth was not significantly affected and no adverse events were reported. Nasal and throat sprays of PVPI as adjuvant therapy may reduce symptoms and viral loads without major alterations in normal bacterial flora growth. Larger trials are needed to confirm.

IndexTerms – Povidone iodine; nasal spray; throat spray; rhinitis; pharyngitis; tonsillitis.

I. INTRODUCTION

Rhinitis, acute pharyngitis, and tonsilitis are common inflammatory diseases of the upper respiratory tract. These can hamper the patient's quality of life (QoL) and lead to significant healthcare utilization and therefore, are an economic burden to the society.(Patel et al., 2020) Though symptoms of rhinitis are usually mild-to-moderate nasal congestion or obstruction, rhinorrhea, sneezing, and pruritus, it can lead to complications, such as asthma, sinusitis, behavioral changes, and psychological impairment.(Liva et al., 2021) Treatment options for rhinitis include intranasal corticosteroids, antihistamines, and decongestants. However, there is a need for newer treatment options as all patients do not respond to the above-mentioned options, and some show side-effects to these treatments. (Patel et al., 2020)

Pharyngitis, defined as an infection or irritation of the pharynx and/or tonsils, typically presents as sore throat along with other symptoms, such as fever, nausea and vomiting, conjunctivitis, etc., depending on the cause.(Acerra, 2023) It is usually caused by a viral infection.(Acerra, 2023; Lewnard et al., 2021) Most cases are self-limiting. Bacterial pharyngitis is also often self-limiting, but there is a higher risk for suppurative and nonsuppurative complications. Sore throat is one of the commonest symptoms resulting in antibiotic misuse.(Lewnard et al., 2021)

Povidone-iodine (PVPI), a commonly used antiseptic disinfectant, in the form of an oral solution is used to gargle and control opportunistic and community-acquired infection. The use of PVPI as a nasal or throat spray gained significant attention during the coronavirus disease 2019 (COVID-19) pandemic.(Lim et al.) Several studies reported the effect of PVPI nasal spray on viral

loads. However, no study has described the effect of PVPI nasal or throat spray on the bacterial flora and viruses in rhinitis and pharyngitis/tonsillitis. These two pilot studies aimed to evaluate the efficacy and safety of PVPI nasal and throat sprays self-administered along with standard care of therapy in patients with rhinitis and tonsillitis/pharyngitis (infections). These studies also studied the effect of the sprays on the normal bacterial flora in the nose and the pharynx/throat.

II. RESEARCH METHODOLOGY

Two, single-center, double-blind randomized pilot studies were conducted to evaluate the efficacy and safety of PVPI nasal and throat sprays in patients with rhinitis and pharyngitis and/or tonsilitis, respectively. The studies were conducted at a private hospital in India.

Both studies were registered prospectively under the Clinical Trials Registry, India (www.ctri.nic.in). As both were pilot studies, a convenience sample of 10 patients was used in each study.

Study 1

Study 1 (CTRI/2022/08/044830) evaluated PVPI nasal spray (NS) in rhinitis.

Participants

The NS pilot study was conducted over 28 days (25 August to 21 September, 2022) on 10 patients aged 18–65 years, with a clinical diagnosis of acute rhinitis and a total nasal symptoms score (TNSS) of 6 or more.

TNSS is the sum of scores for each of nasal congestion, sneezing, nasal itching, and rhinorrhea at each time point, using a 4-point scale (0–3)(Ellis et al., 2015). In the scale, 0 is for no symptoms, 1 for mild symptoms that are easily tolerated, 2 for awareness of symptoms, which are bothersome but tolerable, and 3 is for severe symptoms that are hard to tolerate and interfere with daily activity. TNSS is calculated by adding the score for each of the symptoms to a total score out of 12.

All patients had nasal congestion and one or more of the other symptoms (sneezing, rhinorrhea, and sneezing). Patients who presented with other clinical forms of rhinitis including, but not restricted to, medication-related, vasomotor, and atrophic rhinitis, were excluded from the study. Patients were also excluded if they had signs suggestive of upper airway bacterial infection, had nasal obstruction due to grade II or III septum deviation and/or nasal polyps or other conditions, had undergone sinus surgery within 30 days prior to the beginning of the study, or were intubated at the time of screening. Concomitant chronic or intermittent use of allergen-specific immunotherapy, decongestants, antihistamines, or corticosteroids also excluded patients from the study. Women who were lactating, pregnant, or at a risk of pregnancy were also excluded.

Interventions

The patients were randomly assigned to receive either PVPI (BetadineTM, Win Medicare, India) NS (0.5% w/v) or placebo spray, along with standard care of therapy. Both sprays were self-administered as 2–3 sprays, 3 times daily. All patients were advised to maintain a record of the drug administration, symptoms, and adverse events in a diary.

Evaluations

The patients visited the study center every alternate day over a period of 5 days. During the baseline visit (Day 1), screening was done, and the patients were randomly assigned to either group.

Visit 2 was on Day 3 at the same time (±1 h) of the day as Day 1. Visit 3 was on Day 5 at the same time (±1 h) of the day as visit 2.

During each visit, physical and clinical examinations were done, vitals were recorded, TNSS was determined, adverse events were monitored, and the General Health Questionnaire-12 (GHQ-12)(Hystad and Johnsen, 2020) was used to provide information about an individual's over all well-being by identifying distressing symptoms.

At baseline, nasopharyngeal swab was collected before the administration of the spray. During subsequent visits, nasopharyngeal swab was collected 20 min after administration of the spray.

The samples were analyzed through both molecular and culture methods for syndromic infective aetiology testing of common bacterial and viral causes of rhinitis.

For the molecular testing, the samples were tested for a predefined panel of viruses with 17 strains through qualitative real-time polymerase chain reaction (RT-PCR), using TRU-PCR kit.

In the microbiological assay testing, bacterial profiling of colonizers was done and bacteria were characterized to species level. A visit-wise analysis was done to see if the desired endpoints had been achieved in transient/resident colonizers in subsequent visits.

On Days 3 and 5, the patient's diary of records was reviewed, and patients were assessed/questioned for any adverse events (AE).

Endpoints

Efficacy (primary endpoint) assessment included:

- Reduction in symptoms assessed as a change from baseline in the TNSS scores
- Change in bacterial and viral load in the nasal cavity

Safety and tolerability (secondary endpoint) assessment included:

- The QoL as reported by patients using the GHQ-12 questionnaire
- Number of patients with no nasal congestion, ease in breathing as a sign of tolerability.
- Number of patients experiencing AEs or serious AEs (SAEs) during the study

Study 2

Study 2 (CTRI/2022/08/044866) evaluated PVPI throat spray (TS) in pharyngitis and/or tonsilitis.

Participants

The TS pilot study was conducted over 18 days (25 August to 11 September, 2022) on 10 patients aged 18–65 years, with a clinical diagnosis of acute tonsillitis/pharyngitis.

Patients who wished to continue hot water saline gargle were excluded from the study. Immunocompromised patients and those with known hypersensitivity to the drug substance or any component of the formulation were excluded. The exclusion criteria also included severe sepsis, advanced tonsilopharyngeal disease or infection, known cases of thyroid dysfunction, and those who had undergone thyroidectomy.

Women who were lactating, pregnant, or at a risk of pregnancy were also excluded.

Interventions

The patients were randomly assigned to receive along with standard care of therapy, either PVPI (BetadineTM, Win Medicare, India) TS (0.45% w/v) or a placebo spray. Both sprays were self-administered as 2–3 sprays, 3 times daily. All patients were advised to maintain a record of the drug administration, symptoms, and adverse events in a diary.

Evaluations

The patients visited the study center every alternate day over a period of 5 days. On Day 1 (baseline), screening was done, and the patients were randomly assigned to either group.

Second visit was on Day 3 at the same time (±1 h) of the day as Day 1. On Day 5, at the same time (±1 h) of the day as the first visit, the patient came for visit 3.

During each visit, physical and clinical examinations were done, vitals were recorded, symptoms were evaluated on a 5-point Likert scale (0 = absence of symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms, and 4 = very severe). Sore throat-related QoL (STQoL) questionnaire was used as a tool to determine the QoL. AEs and SAEs were monitored. Ten questions from the STQoL questionnaire were taken into consideration (Table 1).

At baseline, oropharyngeal swab was collected before the administration of the spray. During subsequent visits, the oropharyngeal swab was collected 20 min after administration of the spray. The swab samples were evaluated through both molecular and culture methods for common bacterial and viral causes of pharyngitis. They were tested for a predefined panel of viruses with 17 strains through qualitative RT-PCR using TRU-PCR kit.

For microbiological assay testing, the study protocol necessitated not only pathogen detection but also bacterial profiling of colonizers which were characterized to species level. A visit-wise analysis was done to see if the desired endpoints were achieved in transient/resident colonizers in subsequent visits.

On Days 3 and 5, the patient diary of records was reviewed.

Endpoints

Efficacy (primary endpoint) assessment included:

- Reduction and change in symptoms (sore throat, pharynx discomfort, swelling, redness, pain in swallowing, hoarseness of voice, and foreign object sensation in throat) on a 5-point Likert scale
- Change in bacterial and viral loads in the throat

Secondary endpoint assessments included:

- Time taken in 50% reduction in the main complaints (sore throat, pharynx discomfort, swelling, redness, pain in swallowing, hoarseness of voice, and foreign object sensation in throat)
- Overall time taken for remission of symptoms
- QoL as judged by response to STQoL questionnaire
- Number of participants experiencing AEs or SAEs

As both studies were pilot studies, the sample size was small. The results were, therefore, presented in frequencies and mean ± standard deviation.

III. RESULTS AND DISCUSSION

Each study included 10 patients (4 women and 6 men). Participants' age in the NS study ranged from 21–65 years, whereas that in the TS study ranged from 22–59 years. There were no significant differences in the control and intervention groups in either study at visit 1.

Results of Nasal Spray Study

Symptom relief

At baseline, both groups had similar mean TNSS (7.4 in PVPI group and 7.6 in placebo group, Table 2). However, the percentage reduction from baseline in the mean TNSS on Day 5 was higher in the PVPI group (97.30% versus 84.21% in the placebo group).

Viral and bacterial loads

Influenza A virus and pandemic H1N1 influenza virus were detected in the nasopharyngeal swabs from three patients – two in the PVPI group and one in the placebo group (only from Day 3 sample) (Table 3). Enterovirus was detected in two patients on PVPI. By Day 5, virus was detected in the nasopharyngeal swab sample of only one patient (Influenza A virus: CT28; pandemic H1N1 influenza virus: CT28).

Use of PVPI NS did not damage the normal bacterial flora considerably. By Day 5, the normal flora load was scanty to heavy in all patients irrespective of administration of PVPI or placebo (Table 4).

For one patient in PVPI group, there was moderate growth of pathogen *Klebsiella pneumoniae* and scanty growth of pathogen *Acinetobacter baumannii* from the baseline sample and heavy growth of *Staphylococcus aureus* from the Day 3 sample. No pathogen was detected from the sample taken on Day 5 of PVPI spray administration,

For one patient in the placebo group, there was a moderate growth of pathogen (S. aureus) from the baseline sample. There was no pathogen detected from Day 3 and Day 5 samples.

Quality of life

On an average, both groups reported severe distress due to symptoms at baseline (mean GHQ-12 score of 24.2 in the PVPI group and 25.2 in the placebo group; Table 5). In both groups, compared to baseline, the patient's mean GHQ-12 scores improved considerably by Day 3 and Day 5.

No adverse events were reported by any patient.

One patient from each group reported mild nasal congestion as per TNSS on Day 5.

Results of Throat Spray Study

Symptom relief

At baseline, the mean ± SD Likert score of symptoms in the patients with pharyngitis or tonsilitis was 3.2 ± 0.4 in the group randomized to receive PVPI TS and 2.8 ± 0.4 in the group randomized to receive placebo TS (Table 6, Figure 1).

By Day 5, this had reduced by 93.75% in the PVPI group and by 85.71% in the placebo group.

Viral and bacterial load

Analysis of the throat swabs collected from patients in the PVPI group at baseline showed influenza A virus and pandemic H1N1 influenza virus in two patients and human rhinovirus and human parainfluenza 3 virus in one patient each (Table 7). Viruses were not detected in any of the Day 3 or Day 5 samples in this group.

In the placebo group, at baseline, influenza A virus and pandemic H1N1 virus were detected in two patients and human rhinovirus in one patient. Except in one patient, no virus was detected in samples of Days 3 and 5. Even in that patient, the CT value increased after the placebo spray administration indicating decreased infection/infectivity.

There was growth of normal bacterial flora in all samples collected at baseline (Table 8). Normal flora were scanty, moderate or heavy in all samples collected on Days 3 and 5 as well.

Secondary endpoints

By the Day 3 visit, 50% reduction of the main complaints was reported by one person in the PVPI group and three persons in the placebo group. By Day 5, four out of five patients in PVPI group and three out of four in placebo group reported complete remission of the main complaints.

None of the patients in either group reported any adverse event.

In comparison to baseline scores, the mean scores for the physical aspects of STQoL on Day 3 reduced by a greater percentage in the PVPI group than in the placebo group (66.67% versus 59.46%, Table 9).

PVPI (Betadine) is one of the most commonly available broad-spectrum antiseptics with activity against bacteria, viruses, and fungi. At appropriate concentrations, it is safe to use on mucosal epithelia and has been used as gargles and mouthwashes to fight infections of the mouth and throat.(Stathis et al.) PVPI gargles have led to drop in respiratory infections as well.

In 2006, Kariwa et al(Kariwa et al., 2006) had suggested PVPI products "for gargling and spraying the throat may have a prophylactic effect on SARS during outbreaks". During the COVID-19 pandemic, there was an emergent need to manage transmission risks in the community. This increased the interest in the virucidal properties of PVPI. Some in vitro studies showed encouraging results against SARS-CoV-2(Arefin, 2022) while clinical studies suggested that PVPI nasal spray was safe for topical use but did not possess virucidal activity in COVID-19 patients.(Zarabanda et al., 2022) A preprint article, however, reported that PVPI NS rapidly inactivated SARS-CoV-2 without toxicity concerns.(Liang et al., 2020)

In our NS study, at baseline. viruses were detected in three of five patients in the PVPI group (Table 3). In two of those, no virus was detected in the Day 3 or Day 5 samples. In the other patient whose sample was positive for influenza A virus and pandemic H1N1 influenza virus, though the viruses were detected on Day 5 as well, the CT value remained stable.

PVPI throat spray (at 0.45% formulations) had demonstrated rapid virucidal activities against SARS-Cov-2 in an in-vitro study(Anderson et al., 2020) and fared better than vitamin C for COVID-19 prophylaxis in a large dormitory-based clinical

study.(Seet et al., 2021) In our pharyngitis and/or tonsilitis study, at baseline, viruses were detected in four of the five patients in the PVPI group. On Days 3 and 5, no virus was detected in any sample from patients who received 0.45% PVPI throat spray.
Zarabanda et al(Zarabanda et al., 2022) could not demonstrate virucidal activity of the PVPI nasal spray in COVID-19 patients but the 2% PVPI group had statistically significant improvement in all symptom categories. This group also reported a high rate of nasal burning and pain but the more dilute 0.5% PVPI group reported fewer adverse events on Days 3 and 5. In our study, none of the patients with rhinitis receiving 0.5% PVPI NS nor patients with pharyngitis or tonsilitis receiving 0.45% PVPI TS reported any adverse event or intolerability at any time. The percentage reduction in mean TNSS in rhinitis patients from baseline to Day 5 was better with 0.5% PVPI NS than with placebo (97% versus 84%). Similarly, with 0.45% PVPI TS, the percentage reduction in mean symptom score in patients with pharyngitis and tonsilitis from baseline to Day 5 was better than with placebo (93.75% versus 85.71%).
In an in vitro study, 0.5% PVPI nasal spray formulation has demonstrated time and concentration-dependent bacterial killing against intact biofilm that can cause chronic rhinosinusitis.(Hale et al., 2023)
Commensal bacteria found in the nasal cavity and the pharynx can suppress the colonization of opportunistic pathogens and even directly inhibit or kill competing microorganisms.(Dimitri-Pinheiro et al., 2020) Microbiota dysbiosis is also associated with respiratory viral pathogen invasion leading to respiratory diseases.(Kang and Kang, 2021) As PVPI is a broad spectrum antimicrobial, there may be concerns that PVPI sprays may eliminate the commensal bacteria also. A recent report showed that intranasal PVPI administered immediately prior to surgery was associated with nasal microbial diversity and decreased abundance of Staphylococcus in the post-surgery samples.(Hammond et al., 2022)
Our pilot studies are probably the first two to report the effect of PVPI nasal and throat sprays on commensal bacteria normally harbored in the nose and throat respectively. In both studies, all the samples collected on Day 5, from patients who received either 0.5% PVPI NS or 0.45% PVPI TS, showed colonies of normal bacterial flora implying that growth potential of normal flora was not affected by PVPI treatment.
Patients in both the studies reported a better improvement in QoL after PVPI spray than after the placebo. There was 100% medication adherence and no reported adverse event. In earlier studies, PVPI NS of up to 4.4% concentration have been used in healthy volunteers without adverse events (Gluck et al., 2007)
Our studies are novel as these include topical administration of PVPI in the form of both nasal and throat sprays. These clinical findings strengthen the evidence from in vitro data suggesting virucidal effects of such sprays. In addition, our PVPI sprays allowed commensal bacteria to thrive in the nose and throat.
The limitation of the studies include the small number of patients and the single-center design. These data call for a larger clinical trial involving multiple centers to confirm the benefits of nasal and throat sprays of PVPI.

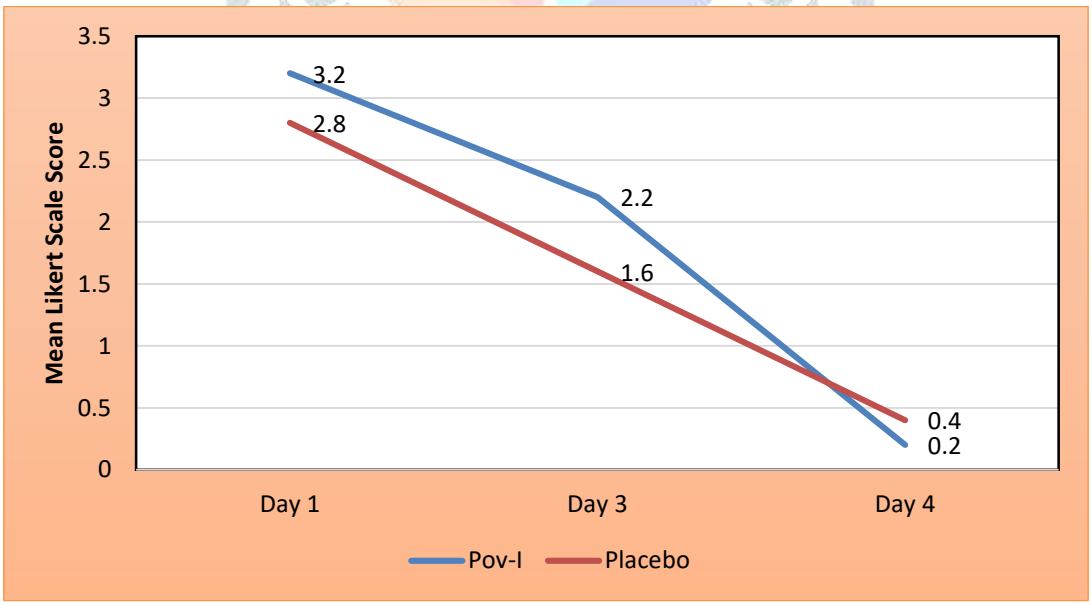

Figure 1. Symptom score on a Likert scale in patients (n=5) with pharyngitis or tonsillitis

Table 1. Questions from the STQoL questionnaire considered

Aspect	Question
Physical	How much your throat hurts, i.e. “burns” or “scratches”?
	Does sore throat make swallowing difficult?
	How much sore throat affects your sleep?
	Does sore throat makes breathing difficult?
	Do you feel exhausted due to sore throat?
Social/Psychic	Are you able to take care about yourself completely?
	How much sore throat affects your concentration?
	Does sore throat interfere with your work?
	Do you have financial losses due to the sore throat?
Environmental	Does sore throat impair your ability to withstand heat or coldness?
STQoL = Sore throat quality of life	

Table 2. Total nasal symptoms score (TNSS) of rhinitis patients receiving a nasal spray

		PVPI Group (n=5)	Placebo Group (n=5)
Mean TNSS (Range)	*V1*	7.4 (6–8)	7.6 (6–9)
	V2	2.2 (1–4)	2.6 (1–5)
	V3	0.2 (0–1)	1.2 (0–3)
% change in mean TNSS from Day 1 to Day 3		-70.27	-65.79
% change in mean TNSS from Day 1 to Day 5		-97.30	-84.21
PVPI group received povidone iodine 0.5% w/v as nasal spray. The placebo group received a placebo as nasal spray. TNSS = total nasal symptom score; w/v = weight by volume; n = number of patients			

Table 3. Viral load in the nasopharynx of patients with rhinitis

Group	Patient no.	Baseline	Day 3	Day 5
PVPI	1	-	-	-
	2	Influenza A virus: CT28; pandemic H1N1 influenza virus: CT28	-	Influenza A virus: CT28; pandemic H1N1 influenza virus: CT28
	3	Influenza A virus: CT32; pandemic H1N1 influenza virus : CT31	-	-
	4	Enterovirus : CT 23	-	-
	5	-	Enterovirus : CT 26	-
Placebo	1	-	-	-
	2	-	-	-
	3	-	Influenza A virus : CT28; pandemic H1N1 influenza virus : CT28	-
	4	-	-	-
	5	-	-	-
CT= cycle threshold value. Cut-off value of CT=35. PVPI group received povidone iodine 0.5% nasal spray 2–3 sprays 3 times daily along with standard care of therapy. Other group received placebo nasal spray 2-3 sprays 3 times daily along with standard care.				

Table 4. Bacterial load in the nasopharynx of patients with rhinitis

Group	Patient no.	Bacteria type	Baseline	Day 3	Day 5
PVPI	1	Pathogen	-	-	-
		Normal	Scanty (*S. epidermidis,* Granulicatella *species)*	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*), Granulicatella species/ Streptococcus like organisms]	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]
	2	Pathogen	-	-	-
		Normal	Scanty (*S. epidermidis, S. haemolyticus*)	-	Scanty (Coagulase -ve Staphylococcus species)
	3	Pathogen	-	-	-
		Normal	Moderate (*S. epidermidis)*	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]	Heavy [Coagulase -ve Staphylococcus species (*S. epidermidis*)]
	4	Pathogen	Moderate (*K. pneumoniae*) Scanty (*A. baumannii*)	Heavy (*S. aureus*)	-
		Normal	Heavy [Coagulase -ve Staphylococcus species (*S. epidermidis*)]	Heavy [Coagulase -ve Staphylococcus species (*S. epidermidis*)]	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]
	5	Pathogen	-	-	-
		Normal	Moderate (*S. epidermidis*)	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]
Placebo	1	Pathogen	Moderate (*S. aureus)*	-	-
		Normal	Heavy [Coagulase -ve Staphylococcus species (*S. epidermidis*)]	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]	Moderate[Coagulase -ve Staphylococcus species (*S. epidermidis*)]
	2	Pathogen	-	-	-
		Normal	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]	-	Moderate [Coagulase -ve Staphylococcus species (*S. epidermidis*)]
	3	Pathogen	-	Scanty (*S. aureus)*	-
		Normal	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]	-	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]
	4	Pathogen	-	-	-
		Normal	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]
	5	Pathogen	-	-	-
		Normal	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]	Scanty [Coagulase -ve Staphylococcus species (*S. epidermidis*)]	Heavy [Coagulase -ve Staphylococcus species (*S. epidermidis*)]; scanty (*Serratia*

					fonticola)

- Indicates no bacteria was detected.

S. = Staphylococcus; K. = Klebsiella; A. = Acinetobacter

PVPI group received povidone iodine 0.5% nasal spray 2–3 sprays 3 times daily along with standard therapy. Baseline swabs were collected on Day 1 before administration of the nasal spray.

Table 5. 12-item general health questionnaire (GHQ-12) scores in patients with rhinitis

	PVPI (0.5% w/v) nasal spray (n=5)		Placebo nasal spray (n=5)	
	Mean ± SD	**Range**	**Mean ± SD**	**Range**
Baseline	24.2 ± 2.32	20-27	25.2 ± 2.64	22–28
Day 3	14.8 ± 1.94	12-18	14 ± 1.26	12–16
Day 5	6.2 ± 0.98	5-8	7.8 ± 1.17	6–9

Table 6. Scoring of symptoms in patients with pharyngitis and tonsilitis on a 5-point Likert scale.

	PVPI group (n=5)			Placebo group (n=5)		
	Mean ± SD	**Median**	**Range**	**Mean ± SD**	**Median**	**Range**
Baseline	3.2 ± 0.4	3	3-4	2.8 ± 0.4	3	2–3
Day 3	2.2 ± 0.4	2	2-3	1.6 ± 0.8	1	1–3
Day 5	0.2 ± 0.4	0	0-1	0.4 ± 0.5	0	0–1
% change in mean baseline to Day 3	-31.25			-42.86		
% change in mean Day 3 to Day 5	-90.0			-75.0		
% change in mean baseline to Day 5	-93.75			-85.71		

SD =standard deviation
PVPI group received povidone iodine (0.45% w/v) throat spray at dose of 2-3 sprays 3 times daily. On the Likert scale, 0 = absence of, 1 = mild, 2= moderate, 3 = severe, and 4 = very severe symptoms.

Table 7. Viral load in the oropharynx of patients with pharyngitis and tonsilitis

Group	Patient no.	Baseline	Day 3	Day 5
PVPI	1	Human rhinovirus: CT26	-	-
	2	Influenza A virus: CT32 Pandemic H1N1 influenza virus: CT32	-	-
	3	-	-	-
	4	Human parainfluenza-3: CT27	-	-
	5	Influenza A virus: CT31 Pandemic H1N1 influenza virus: CT31	-	-
Placebo	1	Influenza A virus: CT20 Pandemic H1N1 influenza virus: CT20	Influenza A virus: CT30 Pandemic H1N1 influenza virus: CT29	Influenza A virus: CT28 Pandemic H1N1 influenza virus: CT28
	2	-	-	-
	3	-	-	-
	4	Influenza A virus: CT25 Pandemic H1N1 influenza virus: CT26	-	-
	5	Human rhinovirus: CT24	-	-

CT= cycle threshold value. Cutoff value of CT=35.
PVPI group received povidone iodine 0.45% throat spray 2-3 sprays 3 times daily along with standard care of therapy. Other group received placebo nasal spray 2–3 sprays 3 times daily along with standard care of therapy.

Table 8. Bacterial load in the oropharynx of patients with pharyngitis and tonsillitis

Group	Patient no.	Microorganism	Baseline	Day 3	Day 5
PVPI	1	Pathogen	-	-	-
		Normal	Heavy (*Strep. mitis/oralis*) Scanty (*Capnocytophaga* species)	Heavy (*Strep. salivarius*)	Heavy (*Strep. pneumoniae*)
	2	Pathogen	-	-	-
		Normal	Heavy (*Neisseria sicca*)	Moderate (*Strep. mitis/oralis*) Scanty (Capnocytophage species) Scanty (*Neisseria sicca*)	Moderate (*Strep. mitis/oralis* & *Strep. thoraltensis*)
	3	Pathogen	-	-	-
		Normal	Heavy (*Strep. pneumoniae*) Scanty (*H. parainfluenzae* & *Sphingomonas paucimobilis)*	Heavy (*Strep. pneumoniae* & *Sphingomonas paucimobilis*)	Moderate (*Strep. mitis/oralis*) Scanty (*E. coli*) Scanty (*H. influenzae*)
	4	Pathogen	-	Moderate (*Strep parasanguinis*)	-
		Normal	Heavy (*Neisseria elongata*)	Moderate (*Neisseria sicca*)	Heavy (*Strep. parasanguinis*) Scanty (*K. pneumoniae* & Capnocytophage species)
	5	Pathogen	-	-	-
		Normal	Scanty (*Enterococcus faecalis*) Scanty (*Strep. mitis/oralis*)	Moderate (*Sphingomonas paucimobilis*) Scanty (*Strep. mitis/oralis*)	Scanty (*Strep. parasanguinis* & *K. pneumoniae*)
Placebo	1	Pathogen	Scanty (*S. aureus*)	-	-
		Normal	Very scanty (group B streptococcus species)	Heavy (*Strep. pneumoniae*) Moderate (Rothia species)	Heavy (*Strep. parasangunis*)
	2	Pathogen	-	-	-
		Normal	Heavy (*Strep. sanguinis*) Moderate (*Strep. salivarius*)	Heavy (Granulicatella species/Streptococcus-like organisms) Moderate (*K. pneumoniae*) Scanty (*Neisseria sicca*)	Heavy (Granulicatella species/Streptococcus like organisms) Scanty (*K. pneumoniae*) Scanty (*Neisseria sicca*)
	3	Pathogen	-	-	-
		Normal	Moderate (*Strep. parasanguinis* & Rothia species)	Moderate (*Kocuria kristinae*)	Scanty (*Kocuria kristinae*) Moderate (*Strep. mitis/oralis*)

			Scanty (*Sphingomonas paucimobilis*)		
	4	Pathogen	-	-	-
		Normal	Heavy (*Strep. parasanguinis*) Scanty (*Sphingomonas paucimobilis*)	Moderate (*Neisseria sicca*) Moderate (*Strep. parasanguinis*)	Moderate (*Strep. parasanguinis*) Scanty (*Granulicatella adiacens* & *Enterobacter cloacae*)
	5	Pathogen	-	-	-
		Normal	Heavy (*Strep. salivarius*) Scanty (*Sphingomonas paucimobilis*)	Heavy (*Strep. mitis/oralis*) Heavy (*Sphingomonas paucimobilis*)	Heavy (*Strep. mitis/oralis*)
- Indicates no bacteria was detected. *Strep.* = *Streptococcus*; *H* = *Haemophilus; E.* = *Escherichia; K.* = *Klebsiella; S.* = *Staphylococcus* PVPI received povidone iodine 0.45% throat spray 2-3 sprays 3 times daily along with standard antibiotic therapy. Baseline (Day 1) swabs were collected before administration of the throat spray.					

Table 9. Scores for STQoL as judged by patients with pharyngitis and tonsilitis

	PVPI (0.45% w/v) throat spray (n=5)		Placebo throat spray (n=5)	
	Mean ± SD	**Range**	**Mean ± SD**	**Range**
Baseline	36.60 ± 1.20	35.00-38.00	37.00 ± 3.35	31.00-41.00
Day 3	20.40 ± 3.26	16.00-26.00	20.80 ± 2.23	17.00-24.00
Day 5	12.20 ± 0.98	11.00-24.00	15.00 ± 1.10	13.00-16.00
% change in mean from baseline to Day 2	-44.26		-43.78	
% change in mean from Day 2 to Day 3	-40.20		-27.88	
% change in mean from baseline to Day 3	-66.67		-59.46	

QoL = quality of life; STQoL = Sore Throat Quality of Life Questionnaire; PVPI = povidone iodine; SD = standard deviation
10 aspects of the STQoL were taken into consideration: 5 physical, 4 social/psychic, and 1 environmental

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Footnotes:

Author contributions:

Conceptualization: RA, HM ; Formal analysis: KS; Funding acquisition: RA; Investigation: HM, AD, LC; Methodology: HM; Resources: RA, AD, LC; Supervision: HM; Validation: RA, AD; Writing – review & editing: HM, RA, KS, AD, LC .

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

KS and RA are employees of Win Medicare Pvt. Ltd which provided the investigational product used in the two studies.

HM, AD, and LC have declared no competing interests.

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Data availability

The data that support the findings of this study are available from the corresponding author, KS, upon reasonable request.

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