

Povidone-iodine for the management of oral mucositis during cancer therapy

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Abstract

Oral mucositis (OM) is a common and often dose-limiting side effect of cancer therapy. Povidone iodine (PVP-I) formulations have been shown to decrease the incidence and severity of OM, but the relevance of these findings remains unclear. The objective of the present study was to review evidence for the use of PVP-I for OM management. An algorithm identified relevant articles published online, and a panel of experts with experience in the management of OM reviewed the findings. Six studies fulfilled the criteria for full review. Two studies provided evidence of moderate quality. Two of the studies with negative findings were confounded by the use of PVP-I concentrations that are too low to be efficacious. The remaining two studies were found to have design flaws. There exists reasonable evidence to support a recommendation for the use of PVP-I in the management of cancer therapy-related OM.

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Introduction

Oral mucositis (OM) is considered one of the most severe non-haematological complications of cancer therapy, affecting more than 40% of patients undergoing some types of chemotherapy and almost all head and neck cancer patients undergoing radiotherapy.^{1,2} The condition is characterized as an inflammatory process that disrupts the mucous lining of the oral cavity and parts of the pharynx. Symptoms include oedema, ulceration and bleeding, with patients often having difficulty swallowing or talking. The associated ulcers and oral lesions that develop can cause significant pain, to the extent where patients may be unable to eat solid food or even ingest liquids at severe stages of OM. In extreme cases, a more serious form called confluent mucositis can arise, lining the patient's mouth and tongue with a white mucus coating. OM is thought to occur independently of oral mucosal infections of viral and fungal aetiology, but it may be exacerbated by such concomitant infections. Therefore, good oral hygiene practices are emphasized to prevent lesions becoming infected with pathogenic microbial flora, of which immunosuppressed patients are likely to be at greater risk.³

Severe OM in patients is a dose-limiting toxicity of cancer therapy as it can necessitate physicians reducing or omitting planned interventions.⁴ In very severe cases, treatment interventions are interrupted and patients may require hospitalization.^{5,6} Such dosage modifications or the discontinuation of recommended chemo/radiotherapy regimens can have a negative impact on clinical outcomes. The development of effective regimens for severe OM is therefore necessary to improve quality of life and treatment outcomes for cancer patients.

Due to heterogeneity in study designs relating to differing aims, methodology and design quality, the evidence available is conflicting and confusing.^{7,8} The Journal of the National Comprehensive Cancer Network (NCCN) published the NCCN Task Force Report: Prevention and Management of Mucositis in Cancer Care in 2008, which makes suggestions for good practice but due to the paucity of strong evidence does not make any recommendations for the treatment of OM.²

In order to provide clearer guidance for clinicians, the Multinational Association of Supportive Care in Cancer (MASCC) in collaboration with the International Society of Oral Oncology (ISOO) conducted a comprehensive assessment of the literature to develop evidence-based and consensus-backed OM clinical practice guidelines.⁹ The MASCC/ISOO guidelines are based on evidence from studies looking at interventions used in

specific cancer treatment regimens.¹⁰ For example, benzydamine is only recommended for head and neck cancer patients receiving moderate dose radiotherapy (up to 50 Gy) without concomitant chemotherapy. This is clinically relevant only to a minority of head and neck cancer patients. However, at least some of the suggested therapeutic agents may not be available in all markets or affordable for all patients. A more universal approach to OM management therefore requires the additional consideration of regulatory and economic factors at play.

While a number of antimicrobial mouthwashes are available, iodophore-based formulations including povidone iodine (PVP-I) have remained popular as antimicrobial agents. PVP-I formulations have a long track record of safe and effective use for the treatment of antiseptics and wound healing.¹¹ The iodine within PVP-I forms a complex with the synthetic carrier polymer polyvinyl pyrrolidone, and in an aqueous medium, free iodine is released. PVP-I complexes release free iodine into the medium and an equilibrium is established, with further free iodine molecules released from PVP-I as iodine-consuming germicidal activity proceeds. This concentration-dependent equilibrium of free iodine to PVP-bound iodine helps to address tolerability issues.¹² The anti-microbial properties associated with iodine involve the inhibition of critical cellular mechanisms via the oxidation of nucleotides, amino acids and fatty acids in cell membranes.¹³ PVP-I has been shown to be effective against both gram-negative and gram-positive bacteria, yeasts, protozoa and viruses.¹⁴ An additional feature of relevance is that there have been no documented cases of bacterial resistance to iodine, likely due to its multiple mechanisms of action.¹⁵ *In vitro* evidence suggests that iodine not only has broad-spectrum antibacterial, antifungal and antiviral effects, but also anti-inflammatory effects that have been proven to inhibit inflammation arising from the host response.¹⁶ These effects have been shown to be clinically relevant in several conditions.¹⁷ For these reasons, PVP-I formulations are extensively used for surgical site preparation, wound management, and feminine care.

Although randomized clinical trials using PVP-I oral gargle for the treatment of OM have been published, the overall implications of these findings have not been thoroughly addressed. Both positive and negative data for the use of PVP-I has been found in the literature. The 2014 MASCC/ISOO guidelines note that studies of PVP-I oral gargle present inadequate or conflicting data, concluding with the designation *No guideline possible*.¹⁰ However, concerns have been raised that at least some of the negative findings reported in the literature may be misleading, as a number of studies have used final concentrations of oral PVP-I that are well below the recommended effective concentration. The current review was undertaken to systematically assess the overall level of evidence present in the literature regarding PVP-I in the treatment of OM.

Materials and Methods

Literature search

A literature search was conducted to identify clinical OM studies of satisfactory relevance. Expert panellists were responsible for reviewing the studies and providing feedback. These panellists are all listed as co-authors of this report and were selected based on their experience in managing OM in a multidisciplinary setting. The method for literature review and assessment was agreed with the authors at the beginning. We excluded review/systematic review articles, reports from duplicated publications or follow-up reports from the same study, clinical practice/chart reviews, *in vitro/in vivo* non-clinical studies, and interventions with povidone iodine as a component of combination treatment, rather than as a single agent (Table 1 and Figure 1).

Inclusion/exclusion criteria

Inclusion criteria were English language publications reporting testing of a PVP-I intervention for OM in humans in relation to cancer, published in a peer-reviewed journal, and indexed in Medline on or before August 31, 2016. Aspects such as selection

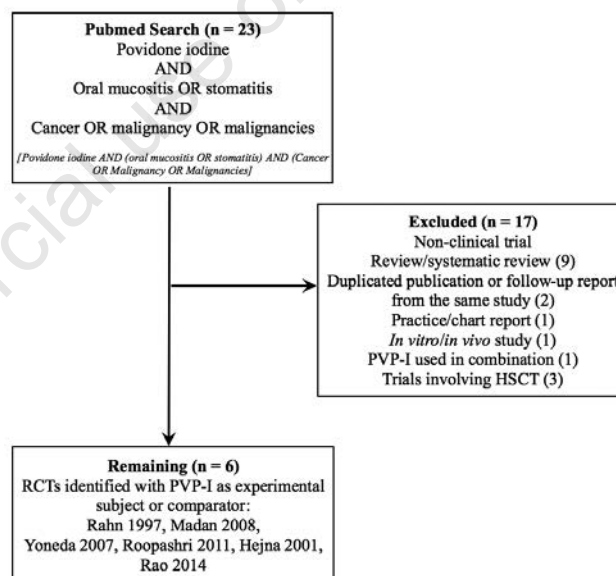


Figure 1. Flow diagram of search results. HSCT, hematopoietic stem cell transplantation; RCT, randomized controlled trials.

Table 1. Inclusion and exclusion criteria for literature search.

Inclusion	Exclusion
Povidone iodine (PubMed term)	Non-clinical trial
Oral mucositis OR stomatitis (PubMed term)	Review/systematic review
Cancer OR malignancy OR malignancies (PubMed term)	Duplicated publication or follow-up report from the same study
Published in peer-reviewed journal (online-only publications permitted for inclusion)	Practice/chart report
All age groups	<i>In vitro/in vivo</i> non-clinical study
	Povidone-iodine as part of combination, rather than single agent
	Trials involving haematopoietic stem cell transplantation

of patients, allocation of patients to treatment groups, therapeutic regimen, study administration, withdrawals from study, patient blinding (randomized controlled trials only), measurements and statistical analysis were evaluated. Upon review of the articles presented, 6 expert panellists (the authors of this review) with extensive experience in the treatment of OM provided their evaluation of: i) the level (quality) of the evidence in the studies supporting PVP-I usage for the treatment of OM; and ii) the class (strength) of recommendation for its usage in OM management (see Addendum for recommendation criteria).

Results

Of the 23 abstracts initially identified in the Medline search, 6 were selected for in-depth review in accordance with the selection algorithm. The studies are summarized in Table 2.

Rahn *et al.* investigated the efficacy of PVP-I for the prophylaxis of mucositis during antineoplastic radiochemotherapy.¹⁸ Forty patients were randomly assigned to a treatment or control group, with all receiving prophylaxis of mucositis with nystatin, dexpanthenol, rutoside and immunoglobulin. In addition, the patients of the treatment group performed rinsing 4 times daily with 1% PVP-I, and the control patients with sterile water. The onset of OM in the control group was at 1.5 weeks from the start of cancer therapy as opposed to 2.25 weeks in the treatment group. The mean total duration of mucositis was 2.75 weeks in patients receiving PVP-I treatment and 9.25 weeks in control patients ($P < 0.001$), with mean area under the curve (AUC) values of 2.5 in treatment patients versus 15.75 for the control patients ($P < 0.001$). Although this study is now somewhat dated as prophylaxis with nystatin is no longer considered standard, the differences observed in this trial were both statistically and clinically significant. It was concluded that rinsing with PVP-I reduced the incidence, time to onset, severity and duration of oral mucositis during antineoplastic radiochemotherapy.

Similarly, in a trial by Madan *et al.*, 80 patients with head and neck cancer undergoing curative radiotherapy were treated with either 0.12% chlorhexidine, 1% PVP-I or salt/soda mouthwashes.¹⁹ It was found that patients receiving PVP-I had significantly lower OM scores compared to both the chlorhexidine and salt/soda groups after 5 weeks of treatment. It was therefore concluded that PVP-I could reduce the severity and delay the onset of cancer therapy-related OM.

Yoneda *et al.* found that a 0.5% solution of PVP-I when included as part of an oral hygiene rinse program using a special electronic dental e-brush with irrigation and suctioning of the mouth significantly lowered the incidence of OM.²⁰ In addition, the proportion of subjects with newly detected opportunistic pathogens was higher in the non-special care group, for which the authors concluded that irrigation with PVP-I is likely to improve patient quality of life and may reduce hospitalization times. Although the study concluded that PVP-I is effective for the treatment of OM, it is important to note that unlike the other five studies, this study used patients with esophageal cancer (which may not always be technically classified as a head and neck cancer), which diversifies the patient *user group*.

A study by Roopashri *et al.* compared benzydamine (0.15%), chlorhexidine (0.2%) and PVP-I (5%), and found evidence of efficacy for all interventions,²¹ but concluded that benzydamine was the superior agent. In fact, the incidence of mucositis was not statistically different in the study and control groups. The observed differences in severity of mucositis and pain did not meet statistical significance. However, the authors did not adequately describe the

overall trial design, particularly in relation to blinding. Despite stating that the *mouth-rinsing regimen was under professional supervision*, it was concluded that compliance with benzydamine was superior. The impact of the findings and the extent of benefit afforded by PVP-I or other treatments in this study is therefore difficult to discern.

The study design employed by Hejna *et al.* tested PVP-I together with amphotericin B (antiseptic agent group) as the comparator for GM-CSF in the prevention and treatment of OM.²² The author concluded that GM-CSF treatment resulted in delayed onset and shorter duration of OM. It is noteworthy that the final concentration of PVP-I oral gargle - though not explicitly stated - is significantly lower than the current recommended concentration of at least 1%. The investigators state 4 mL of betaisodina (7.5% PVP-I) was diluted in 125 mL of water, implying a final concentration of 0.24%. This concentration represents a less than 1 in 4 dilution of the recommended strength.

Rao *et al.* evaluated the efficacy of turmeric in preventing radiation-induced mucositis.²³ In a single-blinded, randomized, controlled clinical trial conducted with head and neck cancer patients requiring 70 Gy of radiation or chemoradiotherapy, patients were randomly assigned to receive either turmeric gargle or PVP-I as an active comparator. The study concluded that gargling with turmeric by head and neck cancer patients undergoing radiation therapy was superior to PVP-I in delaying and reducing the severity of mucositis. PVP-I was used as a comparator at a final concentration approximately 10-fold below that which is recommended. It is therefore likely that the absence of efficacy for PVP-I in this study was entirely due to its low concentration.

In summary, the 3 studies conducted by Rahn, Madan and Yoneda found evidence for the efficacy of PVP-I in alleviating the symptoms of OM. In contrast, the studies by Roopashri, Hejna and Rao did not support PVP-I usage. However, the study by Roopashri suffers from a lack of statistically significant findings, whilst the Hejna and Rao studies used very low concentrations of PVP-I that explain the lack of efficacy.

When the expert panelists who reviewed the studies were asked for their evaluation of the overall level (quality) of evidence considering the strengths of each study, five responded that there was moderate-quality evidence from one or more randomized controlled trials, while the remaining panelist indicated that there was moderate-quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies. Similarly, when asked on the level of recommendation warranted due to this evidence, one panelist gave a recommendation of *strong*, while the remaining five panelists provided a recommendation of *moderate* (taking into account the risk/benefit profile). The slight discrepancy in opinion may have been due to the different clinical settings and standards familiar to the different study coauthors (who were all from different countries).

Discussion

The overall objective of the present study was to provide an objective review of the literature in regards to the use of PVP-I for the management of OM. We sought to critically evaluate 6 of the most relevant clinical trials in the literature that used PVP-I gargle in the treatment or prevention of cancer-related OM, of which the Rahn, Madan, and Yoneda studies were determined as having positive evidence. The Hejna and Rao studies showed negative results, however, this was thought likely to be due to the stated PVP-I concentrations being several-fold below that which is recommended. The study by Roopashri reported only descriptive terms for its

Table 2. Summary of trial designs.

Study	N	Country	Mean age (range)	Eligibility criteria/ patient characteristics	Inten/ primary endpoint	Intervention	Comparator	Statistical significance
Rahn <i>et al.</i> , 1997	40	Germany	Treatment/control 55.3 (35-84)/ 56.2 (37-72)	- Head and neck cancer with radiochemotherapy - Prevention treatment from the start of radiotherapy until 1 week after completion of radiotherapy	Prevention/ Onset, duration and severity of OM	- Nystatin suspension, 4-5 rinses daily - Dexamphenol 1 tablet 4 times daily - Betaisodina 1:8 dilution 100 mL 4 times daily (final estimated concentration: 1.25% PVP-I solution)	Sterile water	Onset 0.05- (U-test), Recovery 0.001- (U), Severity 0.005- (Chi-sq), Duration 0.001- (U), AUC 0.001- (U)
Madan <i>et al.</i> , 2008	80	India	4 arms Chlorhexidine/PVP-I/ Salt-soda/control 57.35/54.25/58.2/054.45	- Head and neck cancer with radiotherapy - Prevention treatment for oral mucositis over 6 weeks of radiotherapy	Prevention/ Onset and severity of OM	10 mL of one of below mouth wash 2 min twice daily or control (plain water) • 0.12 % Chlorhexidine • 1% PVP-I • Salt/soda	Plain water	OM severity (PVP-I vs Ctrl): Week1 P=0.014; OM sev (PVP-I vs Salt/soda): Week4 P=0.016 Onset: P=0.005
Yoneda <i>et al.</i> , 2007	40	Japan	Treatment/control 62.6 (49-81)/ 8.3 (56-79)	- Esophageal cancer with 5FU and cisplatin chemotherapy - Prevention treatment of oral mucositis with oral care and PVP-I during chemotherapy	Prevention/ Incidence of OM, opportunistic pathogen infection	- Special oral care by dentist followed by 20 ml of PVP-I oral wash (0.5% PVP-I, Iodine Gargle)	Non-care	OM frequency: P=0.048 <i>Streptococci</i> in non-special care group: P=0.034; Opportunistic infection: P=0.019
Roopashri <i>et al.</i> , 2011	1100	India	Mean age not specified (30-70)	- Patients with head and neck malignancies who were planned for RT with a daily dose of 220 CCy for a period of six weeks, with a total dose of 6600 CCy; 30 fractions	Treatment/ OM grade, pain score	One of the following treatments: • Benzylamine hydrochloride (0.15%) • Chlorhexidine (0.2%) • Povidone iodine (5%)	Distilled water	Data given in a descriptive manner for OM and pain grade, improvement in PVP-I group over placebo in Weeks 3, 4, 5 and 6.
Hejnia <i>et al.</i> , 2001	31	Austria	GM-CSF/antiseptic 58 (39-77)/ 73 (48-80)	- Patients with colorectal, gastric cancer, pancreatic, breast cancer or cholangiocellular cancer receiving FU-based chemotherapy - AA group significantly older, poorer PS, alcohol ingestion, smoking, poorer oral hygiene	Treatment/OM grade, number of lesions	- GM-CSF mouth wash; or - 4 mL PVP-I in 125 mL of water (Betaisodona Mund-Antiseptikum); estimated final PVP-I concentration: 0.3% solution)	PVP-I 7.5%, 4 ml diluted in 125 ml = 0.24% PVP-I final concentration	Concentration of PVP-I used was too low for the study to be of relevance
Rao <i>et al.</i> , 2014	80	India	PVP-I/turmeric 55.08±13.14 56.8±11.73	- Head and neck cancer (according to TNM classification) scheduled to receive radiotherapy or chemoradiotherapy	Prevention/ Onset and severity of OM	- Mouthwash containing 400 mg turmeric; or - PVP-I solution diluted 1:100 (Betadine 1 mL and 100 mL water; estimated final concentration: 0.1% PVP-I solution)	0.1% PVP-I	Concentration of PVP-I used was too low for the study to be of relevance

results, with no statistically significant conclusions. PVP-I gargle is marketed for oral care at 1% concentration, and it appears that a common flaw in methodology is its inappropriate dilution during clinical application to levels that would be non-efficacious. In contrast, for the randomized studies with concentrations ranging between 0.5-1% PVP-I, all three showed the effective alleviation of OM-related symptoms. The differing conclusions of the studies may be due to differences in the tumor types, patient populations and chemo/radiotherapy regimens used. These differences were not always discernable. For example, the Yoneda study listed the 5-FU regimen used but not the dosage of radiotherapy, while the Hejna study simply stated, *patients who had undergone radiotherapy of head and neck were eligible, if at least 6 weeks had elapsed since termination of therapy and the resolution of acute toxic effects of treatment*. In contrast, the Madan and Rao studies used identical radiation treatment regimens (2 Gy per day, five times a week without any intended gaps for a planned target dose of 70 Gy (7 consecutive weeks). It is recommendable for future reports to list the full details of chemo/radiotherapy regimens used in order to better determine the causes for distinct findings.

The oral mucosa has a rapid rate of cellular turnover, and is therefore highly susceptible to cancer treatment-related toxicity caused by chemotherapy and ionizing radiation.²⁴ Complications with inflamed tissue can also arise due to the diverse and complex microflora that colonizes the oral cavity. The effective treatment of OM therefore likely requires both the inflammatory and microbial aspects to be addressed.²⁵ As an agent that exhibits potent and clinically relevant anti-inflammatory and antimicrobial properties,^{14,17} PVP-I formulations could therefore impact the pathophysiological mechanisms responsible for OM.

Strong mechanistic rationale exists for the application of PVP-I in treating the symptoms of OM. *In vitro* and *in vivo* studies have revealed potent anti-inflammatory, antiseptic, anti-oedematous, and anti-hemostatic effects in a wide range of models. The anti-inflammatory effects of PVP-I on microbial-induced cytokine generation have been observed in various cell lines, including human neutrophils. TNF- α is an important mediator of inflammation and its dysregulation is implicated in various chronic diseases. It was demonstrated that PVP-I suppresses TNF- α release from human neutrophils in response to stimulation by *Staphylococcus aureus* and Respiratory Syncytial Virus epitopes. Similarly, the enzyme β -galactosidase is considered a marker of bacterial activity during the inflammatory process. Treatment with varying concentrations of PVP-I has been shown to reduce β -galactosidase activity in *Escherichia coli* cultures and supernatant.²⁶

A position paper released by the European Wound Management Association (EWMA) notes the broad spectrum of PVP-I activity against both gram positive and negative bacteria, fungi, endospores and viruses.²⁶ While evidence of cross-resistance to antiseptics and antibiotics has been documented for many agents, acquired resistance and cross-resistance has been rarely reported for iodine when used for specific indications.²⁷ This lack of resistance is thought to be due to the diverse mechanisms through which iodine exerts its effects.

PVP-I is also likely to have anti-oedematous effects. A single-blind randomized study was conducted to evaluate facial swelling in postoperative patients over varying time intervals. In the treatment group, a 0.5% PVP-I solution at a concentration of 0.5 mg/mL caused a significant reduction in postoperative swelling compared to the control group ($P < 0.01$). This effect of PVP-I was suggested to be due to its inhibitory effect on leukotriene B4 and leukocyte extravasation.²⁸

Further investigation into the anti-hemostatic effects of PVP-I have similarly revealed important findings. In a study of fresh

bleeding following irrigation of the extraction socket in patients that have had a tooth removed, 19 of 25 patients in the treatment group showed spontaneous cessation of bleeding upon application of PVP-I, which was observed in only 5 of the 25 patients irrigated with saline. These observations were made prior to drying the socket with gauze following which the sockets were compressed. Post-extraction bleeding was determined to be significantly ($P < 0.01$) controlled by PVP-I treatment as compared to saline.²⁹ The anti-hemostatic effect may help patients with bleeding from severe mucositis and this needs to be investigated further.

From these findings, it appears that the benefits of PVP-I for the treatment of inflammatory conditions such as OM could be broader than its effects as an anti-microbial agent. The long track record of safe and efficacious use of PVP-I in clinical settings is also an advantage for further clinical investigation.

The current options available for OM management in clinical trials and clinical practice are severely limited. Keefe *et al.* has encouraged the pharmaceutical industry to refocus its efforts on developing such agents in areas of unmet need, including OM and chemotherapy-induced nausea/vomiting.³⁰ The considerable unmet medical needs that remain for OM necessitate the investigation of a wider range of therapies.

The authors suggest that there is moderate scientific evidence for benefit provided by PVP-I in the management of OM; however, additional studies are encouraged. The authors also agree that based on the available evidence, PVP-I can be recommended for the prevention and treatment of OM.

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