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SUMMARY WITH CRITICAL APPRAISAL

Benzydamine for the Treatment of Oropharyngeal Mucositis from Radiation Therapy: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

MASCC/ISOO	Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology
RCT	randomized controlled trial

Context and Policy Issues

Oral mucositis is the most common pain syndrome experienced by patients receiving cancer treatment.¹ The Common Terminology Criteria for Adverse Events defines oral mucositis as “a disorder characterized by ulceration or inflammation of the oral mucosa”.² It can be caused by either chemotherapy or radiation therapy, and it occurs in almost all patients with head and neck cancer receiving treatment with radiation therapy.¹ Mucositis can also occur in the pharynx, larynx and esophagus, and in other areas of the gastrointestinal tract.³

Oral mucositis secondary to radiation therapy typically develops after 2-3 weeks.¹ Radiation causes loss of stem cells in the basal layer of the skin. Subsequently, inadequate production of new cells to replace those that are lost through normal sloughing contributes to the development of mucositis. Oral mucositis can be severely painful and lead to reduced oral intake and poor nutrition. Although some form of mucositis occurs in nearly all patients receiving radiation treatment for head and neck cancer, minimizing the volume of normal mucosal tissues that receive radiation and minimizing the use of concurrent chemotherapy is the most effective way to reduce the severity of mucositis.⁴ Despite advances in methods of delivery of radiation therapy aimed at minimizing mucositis, it remains a common and important potential adverse effect of cancer therapy.¹

Typical management strategies include stringent oral hygiene, dietary restrictions, treatment of superinfections, analgesics for pain, and topical agents. Topical agents that have been studied in management of oral mucositis include the tricyclic agent doxepin, “miracle” or “magic” mouthwashes which are made using a combination of ingredients (including 2 or more out of topical anesthetics, antacids, diphenhydramine, nystatin, dexamethasone and tetracycline), mucoadhesive hydrogel, and benzydamine oral rinse. Palifermin is a keratinocyte growth factor given by injection that has shown to decrease incidence and duration of severe mucositis vs placebo. The use of palifermin is generally limited by its high cost.⁴ Low-level laser therapy is another potentially effective approach that can be limited by cost of equipment and labour-intensive treatment regimens.^{3,5}

Benzydamine is a nonsteroidal anti-inflammatory agent with anti-inflammatory, analgesic, anesthetic, and antimicrobial activity.⁴ Benzydamine is available in Canada as a 0.15% oral solution for use as a gargle or rinse. Localized numbness (10%) and burning/stinging (8%) are common adverse reactions.^{6,7}

The objective of this report is to review the evidence and guidelines for use of benzydamine rinse for treatment of oropharyngeal mucositis secondary to radiation therapy.

Research Questions

1. What is the clinical effectiveness of benzydamine oral rinse (0.15%) for the symptomatic relief of oropharyngeal mucositis caused by radiation therapy?

2. What are guidelines informing the use of benzydamine oral rinse (0.15%) for the symptomatic relief of oropharyngeal mucositis caused by radiation therapy?

Key Findings

There is no evidence supporting the clinical effectiveness of benzydamine oral rinse for treatment of oropharyngeal mucositis caused by radiation therapy. A high quality systematic review identified two poor quality randomized controlled trials; these studies did not show a difference between benzydamine and placebo for improvement in oral mucositis.

Available guidelines for the management of mucositis secondary to cancer therapy did not address the use of benzydamine oral rinse for treatment of oropharyngeal mucositis.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2008 and August 28, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients of any age (inpatient or outpatient setting) with oropharyngeal mucositis caused by radiation therapy
Intervention	Benzydamine 0.15% oral rinse
Comparator	Standard care, placebo
Outcomes	Clinical effectiveness i.e., benefit (relief of symptoms); harm (irritation; numbing of the tongue)
Study Designs	HTA/Systematic Reviews/Meta-Analyses, Randomized Controlled Trials, Non-randomized Studies, Guidelines

HTA= Health technology assessment

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2008. Primary studies captured within an included systematic review, systematic reviews that included studies that were fully captured in more recent or more comprehensive systematic reviews, and guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

Quality of included studies was assessed by one reviewer. The included systematic reviews were critically appraised using AMSTAR 2,⁸ and included guidelines were assessed with the AGREE II instrument.⁹ Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 131 citations were identified in the literature search. Following screening of titles and abstracts, 113 citations were excluded and 18 potentially relevant reports from the electronic search were retrieved for full-text review. Eight potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 24 publications were excluded for various reasons, and two publications met the inclusion criteria and were included in this report. These comprised one systematic review,⁵ and one evidence-based guideline.³ Appendix 1 presents the PRISMA¹⁰ flowchart for study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2

Study Design

One systematic review published in 2010 with a search date of June 1st 2010 met eligibility criteria for this review.⁵ Thirty-two RCTs were included in the systematic review. Two of those RCTs are relevant to this report, published in 1985 and 1987. Results were pooled in a meta-analysis.

One guideline, developed by the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO), met eligibility for this review.³ Methods are described in greater detail in two related publications.^{11,12} A series of systematic reviews were conducted to inform guideline development. Studies published up to December 31st 2010 assessing interventions for management (prevention or treatment) of mucositis were included in their evidence reviews. Inclusion was not restricted by study design. Evidence is rated considering quantity and quality for each intervention, as level I (highest level) through IV. Guidance is categorized as 'recommendations' (level I or II evidence), 'suggestions' (level III or IV evidence), or 'no guideline possible' (indicating a lack of evidence, or inability to reach consensus).

Country of Origin

The systematic review was conducted in the United Kingdom. The two relevant RCTs included within the review were conducted in the United States.⁵

The guidelines are intended for international use.³

Patient Population

The systematic review included adults with mucositis secondary to chemotherapy or radiation. One of the two included RCTs assessing effectiveness of benzydamine was in adults receiving radiation for treatment head and neck cancer (n=67); the systematic review excluded data from three patients who did not have mucositis at study start. The second RCT was conducted in adults receiving either chemotherapy or radiation therapy; the proportion in each subgroup was not specified (n=44).⁵

The guidelines are intended to apply to anyone with or at risk of mucositis secondary to any cancer therapy.³

Interventions and Comparators

The systematic review included studies assessing any intervention for treatment of oral mucositis compared to any active treatment, no treatment, or placebo. The two relevant RCTs included within the SR assessed effectiveness of benzydamine 0.15% solution versus placebo. Dosing of the oral rinse was every 3 hours during the day in the first RCT, and 15 mL swish and hold for 1 minute every 2 hours, minimum five doses per day in the other.⁵

The systematic reviews that were conducted to inform the guidelines assessed any intervention for the treatment of oral mucositis.³

Outcomes

The relevant outcome assessed in the Cochrane review was improvement in mucositis. Outcomes were reported in the included RCTs as clinician-assessed improvement according to an unvalidated 4-point severity scale on day two or three in one study, and patient assessment of pain relief at day one in the other.⁵

The relevant outcomes of interest for the systematic reviews that informed the guidelines were 'mucositis-related outcomes', including pain.³

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

The systematic review was of high quality overall. Study selection, data extraction and quality assessment were done independently by two reviewers, a comprehensive literature search was thoroughly described, inclusion was not restricted by publication status, and study characteristics and quality assessment were well-reported. Results of the two relevant RCTs were pooled in a meta-analysis despite substantial statistical heterogeneity; this was not adequately addressed in the interpretation of the results. The two relevant RCTs included within the SR were deemed to be at high risk of bias according to the investigators.⁵

The MASCC/ISOO guidelines are of moderate quality. The scope and purpose of the guidelines are clear, the systematic reviews of the evidence and method of guideline development are well-described, and recommendations are clearly presented. Limitations included lack of inclusion of views and preferences of target population and other relevant professional groups, and an inadequate description of barriers and facilitators to application of guidelines.³

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical effectiveness of benzydamine

The systematic review combined the results of two RCTs comparing benzydamine to placebo in a meta-analysis for the outcome of 'improvement in oral mucositis'. Neither of the included RCTs found a statistically significant effect. The pooled RR of 1.22 (95% confidence interval 0.94 to 1.60) was also not statistically significant, and there was substantial statistical heterogeneity. No conclusions regarding benzydamine's effectiveness for treatment of mucositis were stated.⁵

Guidelines

The MASCC/ISOO guidelines did not provide any recommendations, suggestions, or evidence surrounding the use of benzydamine for the treatment of oral mucositis. The guidelines do recommend the use of benzydamine mouthwash for the prevention of oral mucositis in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy.³

Limitations

No high-quality studies assessing the clinical effectiveness of benzydamine rinse for treatment of oropharyngeal mucositis were identified. The RCTs included in the systematic review were deemed to be at high risk of bias by the authors. Additionally, they were conducted over 30 years ago which may limit applicability.

Although the scope of the guidelines included in this report encompasses the use of interventions for treatment of oral mucositis, the use of benzydamine for treatment is not specifically addressed by these or any other guidelines.

Conclusions and Implications for Decision or Policy Making

A systematic review and an evidence-based guideline were included in this review.

There is no evidence supporting the effectiveness of benzydamine rinse for symptomatic relief of oropharyngeal mucositis caused by radiation therapy. Poor quality RCT evidence does not suggest that benzydamine rinse is more effective than placebo for treatment of oral mucositis.

Available evidence-based guidelines do not specifically address the use of benzydamine rinse for relief of symptoms of mucositis.

The MASCC/ISOO guidelines for management of mucositis secondary to cancer therapy recommend or suggest other interventions for treatment of symptoms of oral mucositis, including topical and systemic opioid analgesics and doxepin 0.5% mouthwash. With respect to prevention of mucositis, the guidelines recommend the use of benzydamine rinse in patients with head and neck cancer receiving moderate dose radiation therapy.³ However, a Cochrane systematic review concluded that evidence surrounding the use of benzydamine for prevention of mucositis was weak and unreliable.¹³

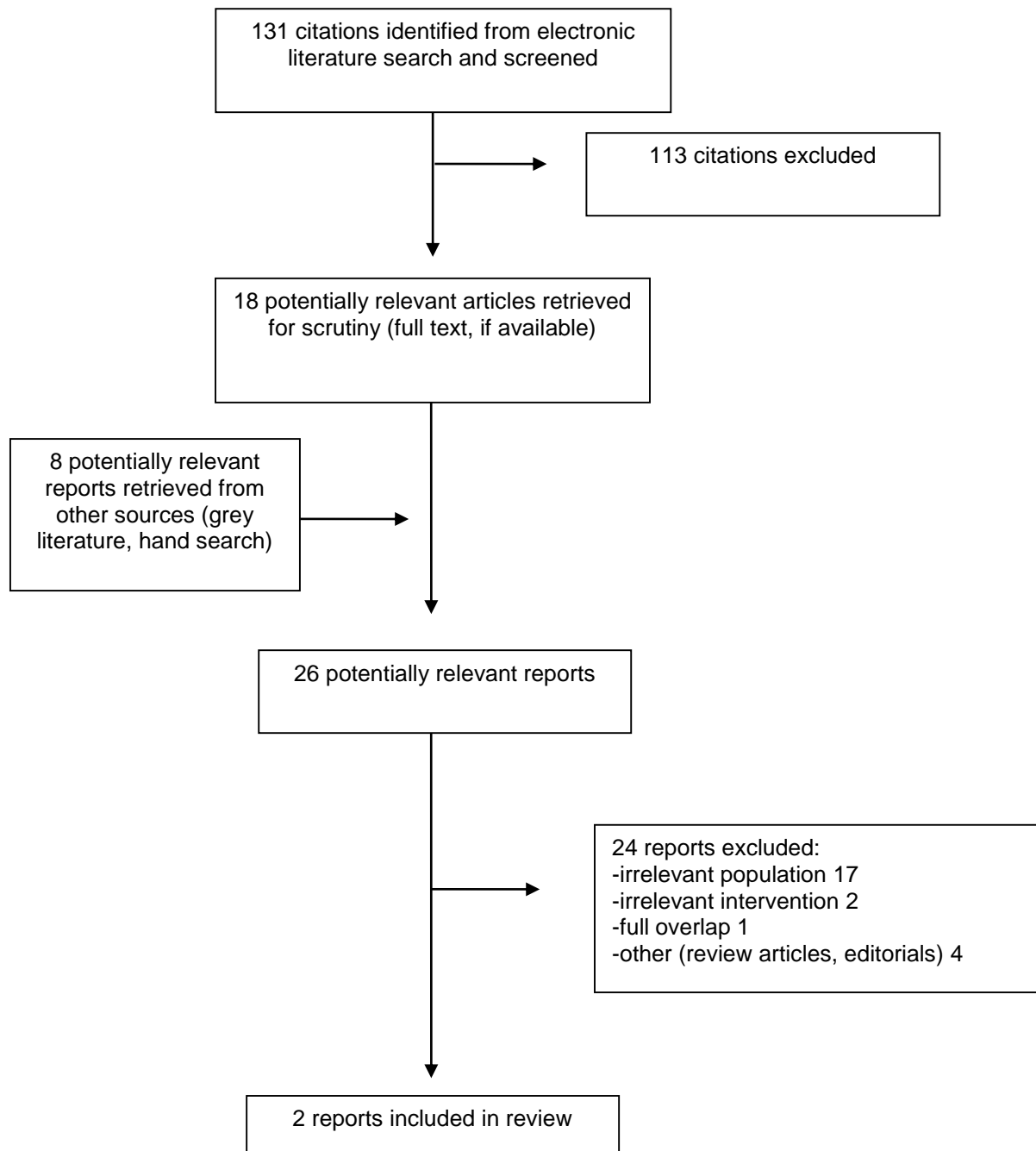
Despite the common and potentially severe nature of oropharyngeal mucositis secondary to radiation therapy, there is a lack of evidence supporting safe and effective treatment

strategies. New, high-quality studies assessing the effectiveness of benzydamine rinse for symptomatic relief of oropharyngeal mucositis secondary to radiation therapy would reduce uncertainty.

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Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Clarkson 2010 ⁵ United Kingdom	32 RCTs (2 relevant)	Adults with mucositis secondary to radiotherapy (1 RCT) for head and neck cancer; adults with mucositis secondary to radiotherapy or chemotherapy (1 RCT)	In both relevant RCTs: Benzydamine 0.15% oral solution versus placebo	Improvement in mucositis (Clinician-assessed improvement on day 2/3 in 1RCT; patient assessment of pain-relief on day 1 in the other)

RCT = randomized controlled trial

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation
Lalla, 2014 ³					
Users not defined; patients with or at risk for mucositis secondary to cancer treatment	Interventions used for management of mucositis	Occurrence of mucositis, mucositis-related outcomes (such as pain)	Series of systematic reviews	Study quality was assessed independently by two reviewers; interventions were assigned a level of evidence considering quantity and quality of evidence (levels I-IV)	Provisional guidelines were formed based on level of evidence, and finalized at a consensus conference

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2⁸

Strengths	Limitations
Clarkson, 2010 ⁵	
Study selection, data extraction and risk of bias assessment were done independently in duplicate Comprehensive literature search Not restricted by publication status Study characteristics and quality assessment thoroughly reported	Substantial statistical heterogeneity of results pooled in meta-analysis was not addressed The two relevant RCTs included within the SR were deemed to be at high risk of bias

RCT = randomized controlled trial; SR = systematic review

Table 5: Strengths and Limitations of Guidelines using AGREE II⁹

Strengths	Limitations
Lalla, 2014 ³	
Clear scope and purpose Methods of gathering and applying evidence were well-described Method of guideline development was well-described Recommendations were clearly presented	Lack of inclusion of views and preferences of target population Lack of inclusion of all relevant professional groups inadequate description of barriers and facilitators to guideline application

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Clarkson, 2010 ⁵	
Meta-analysis of two RCTs: Improvement in mucositis with benzydamine versus placebo RR 1.21 (95% CI 0.94 to 1.60), I ² = 90%, P = 0.14	<i>"There is limited evidence from two small trials that low level laser treatment reduces the severity of the mucositis...Further, well designed, placebo or no treatment controlled trials assessing the effectiveness of interventions investigated in this review and new interventions for treating mucositis are needed."</i> (pp 2) No conclusions specific to the effectiveness of benzydamine were stated.

CI = confidence interval; RCT= randomized controlled trial; RR= relative risk

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Lalla, 2014 ³	
There were no recommendations or suggestions relevant to treatment of oral mucositis with benzydamine; only prevention	Not applicable