Effectiveness of sucking ice cubes to prevent and reduce the severity of oral mucositis

Efektivitas mengisap es batu untuk mencegah dan mengurangi keparahan mucositis mulut

[1]Yessy Novianti, [2]Tenny Setiani Dewi
[1]Oral Medicine Study Program
[2]Department of Oral Medicine,
Faculty of Dentistry, Padjadjaran University
Bandung, Indonesia
Corresponding author: **Yessy Novianti,** e-mail: **yessy21001@mail.unpad.ac.id**

ABSTRACT

Oral mucositis is an inflammation that occurs in the oral mucosa due to side effects of cancer therapy in the form of chemotherapy, radiotherapy, and chemoradiotherapy. The condition of severe oral mucositis can worsen the prognosis of cancer treatment and reduce the patient's quality of life. One method to reduce the severity of oral mucositis is cryotherapy. The purpose of this systematic review is to review the effectiveness of oral cryotherapy using the ice cube method in preventing and reducing the severity of oral mucositis. This review was conducted using PRISMA guidelines. Article searches were conducted using five electronic databases, namely PubMed, Science Direct, Cochrane, Scopus and Springer Link for articles published 2017-2022 using specific keywords. The criteria were limited to randomized controlled trial in human, full text, and in English only. The results were the incidences of oral mucositis, the severity and pain scores in patients. The study quality graded using the Modified Jadad Scale. There were seven articles that met the eligibility criteria for analysis. It is concluded that the majority of studies prove that oral cryotherapy using ice cubes is effective in preventing and reducing the severity of oral mucositis.

Keywords: ice cubes, cryotherapy, oral mucositis

ABSTRAK

Mukositis oral adalah peradangan yang terjadi pada mukosa mulut akibat efek samping terapi kanker berupa kemoterapi, radioterapi, dan kemoradioterapi. Kondisi mukositis yang parah dapat memperburuk prognosis pengobatan kanker dan menurunkan kualitas hidup pasien. Salah satu metode untuk mengurangi keparahan mukositis oral adalah krioterapi. Tujuan dari tinjauan sistematis ini adalah untuk meninjau efektivitas krioterapi oral dengan metode es batu dalam mencegah dan mengurangi keparahan mukositis oral. Tinjauan ini dilakukan dengan menggunakan pedoman PRISMA. Pencarian artikel dilakukan dengan menggunakan lima database elektronik, yaitu PubMed, Science Direct, Cochrane, Scopus, dan Springer Link untuk artikel yang diterbitkan tahun 2017-2022 dengan menggunakan kata kunci tertentu. Kriteria artikel dibatasi pada uji coba terkontrol acak pada manusia, teks lengkap, dan hanya dalam bahasa Inggris. Hasil dari penelitian ini adalah insiden mukositis oral, tingkat keparahan dan skor nyeri pada pasien. Kualitas penelitian dinilai dengan menggunakan Skala Jadad yang dimodifikasi. Terdapat tujuh artikel yang sesuai kriteria kelayakan untuk dianalisis. Disimpulkan bahwa sebagian besar penelitian membuktikan bahwa krioterapi oral menggunakan es batu efektif dalam mencegah dan mengurangi keparahan mukositis oral.

Kata kunci: es batu, krioterapi, mukositis oral

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INTRODUCTION

Oral mucositis is an inflammation of oral mucosa due to cancer therapy, characterized by erythema, ulceration, swelling and pain.[1–6] Oral mucositis occurs during or after cancer therapy in the form of chemotherapy, radiotherapy or a combination of both, including conditioning prior to bone marrow transplantation.[4,5,7–10] The incidence of oral mucositis in chemotherapy patients is around 40-80% in head and neck cancer radiodiotherapy patients.[3–5,8,9] The clinical symptoms are dry mouth, loss of taste, burning sensation and pain.[11]

Oral mucositis has a negative impact which can decrease patient's quality of life.[5,12] The pain of oral mucositis may cause difficulty in eating, chewing, speaking, and brushing teeth.[3] These conditions lead to nutritional deficiencies, weight loss, dehydration and disruption of optimal chemotherapy regimens. Other complications are increased consumption of narcotics, prolonged hospitalization, the usage of total parenteral nutrition and the occurrence of sepsis which can lead to death.[4,5,9,12–14]

The higher severity of oral mucositis, the more painful and worse the patient's condition is. There are several instruments used to assess the severity of oral mucositis such as the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), the toxicity criteria of the Radiation Therapy Oncology Group (RTOG), the European Organization for Research and Treatment of Cancer (EORTC), the World Health Organization (WHO) scale, the Oral Mucositis Assessment Scale (OMAS), and Children's International Mucositis Evaluation Scale (ChIMES).[1,5,6,15] Instruments for pain assessment are Numerical Rating Scale (NRS) and Visual Analog Scale (VAS).[14,16,17]

Management of oral mucositis is pivotal to reduce pain, prevent secondary infection, support nutrition and improve patient's quality of life.[5] One of them is the oral cryotherapy, with the principle of application of cold temperatures to the mucosal tissue. Oral cryotherapy is

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a non-pharmacological therapy by sucking ice chips in the mouth.[2,6,15,18] This technique is simple, easy to do, inexpensive, and easy to get the substances. The objective of this systematic review is to evaluate the effectiveness of sucking ice cubes in preventing and reducing the severity of oral mucositis. This systematic review can be a complement and updates on the latest scientific information regarding oral cryotherapy.

METHODS

This systematic review was performed according to the *preferred reporting items for systematic review and meta-analysis* (PRISMA) guidelines (Fig.1). The topics were arranged using *population, intervention, comparison, outcome* (PICO). The population were patients with oral mucositis due to cancer therapy in the form of chemotherapy, radiotherapy, a combination of both, and conditioning prior to bone marrow transplantation. The type of cancer and the degree of malignancy are not distinguished on population.

The intervention was the application of ice cubes, both flavored and unflavored, for oral mucositis therapy. The comparison was the positive or negative control group. The outcome was the incidence and the severity of oral mucositis. Post-therapy target was assessed with oral mucositis assessment instruments (OMAS, WHO, NCI-CTC, CHIMES) and pain assessment instruments (VAS, NRS).

The inclusion criteria were limited to clinical trial studies of sucking ice cubes for oral mucositis therapy, human studies, available and accessible full text, in English, article which published in the last 5 years (2017-2022). The articles were excluded if irrelevant to the topic, duplication, literature reviews, incomplete manuscripts and articles not in English.

Relevant articles were searched electronically using five databases namely Pubmed, Science Direct, Cochrane, Scopus, and Springer Link. The keywords used were ((((("oral mucositis"[MeSH Terms]) AND ("ice cubes" [All Fields]))) OR ("ice chips" [MeSH Terms]))) OR ("oral cryotherapy" [MeSH Terms])).

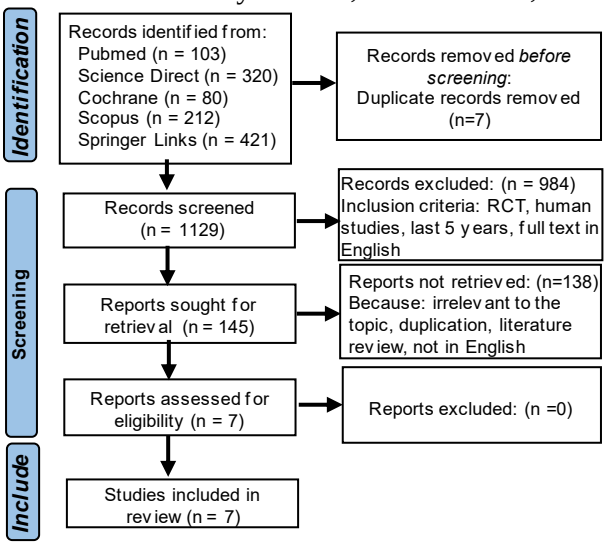

Figure 1 PRISMA flow diagram

The study quality graded using the Modified Jadad Scale by the authors (TSD and YN). The MJS consists of eight questions, as if was the study described as a randomized, was the method of randomization appropriate, was the study described as blinded, was the method of blinding appropriate, was there a description of withdrawal and drop-out, was there a clear description of the inclusion and exclusion criteria, was the methods used to assess side effects described, was the method of statistical analysis described. The conclusion of the article's quality assessment refers to the total score of each article. The maximum score is 8 (eight) and the minimum score is 0 (zero). High quality is shown by a total score 4-8, means that the quality of the article is good, while a total score 0-3 means that the quality of the article is poor or low.[19]

The selected articles are scrutinized for relevance to the research objectives made by the authors. Furthermore, the author (YN) extracted the relevant data and selected the important information. The extracted information includes population (author, year, country, number of samples, type of cancer and cancer therapy), type of intervention (sucking ice cubes), comparison group and study results (incidence and severity of oral mucocositis). The authors (TSD and YN) discussed the extracted data and made decisions to evolve the final recommendation in this study. In case of differences of opinion, discussions and decision-making are carried out accordingly to reach a mutual agreement. There is no difference in determining which articles qualify for review, the extracted data and the assessment of the risk of bias.

RESULTS

The article searching process according to PRISMA guidelines (Fig.1). There were 145 articles found by electronic searching. Each article was scrutinized based on the inclusion and exclusion criteria, found that 138 articles were excluded as it did not meet the criteria and left 7 appropriate articles for further review. According to MJS, it was concluded that all the articles to be reviewed have high quality. The details of the quality assessment scores for 7 selected articles were presented in table 1. The data and information related to population such as author, year, country, sample size, type of cancer, cancer therapy and type of oral cryotherapy are extracted and summarized in a table 2. The general summary of the article was presented in table 3.

Incidence was counted based on total patients who had oral mucositis after receiving cancer therapy. In six

studies reported a reduction in incidence of oral mucositis in the intervention group. Mishra et al., reported that the incidence of oral mucositis in children who sucked on flavored ice cubes (honey and tulsi) was lower than children who sucked water ice cubes on day 5 and on day 15 ($p<0.001$) after chemotherapy.[20]

Moreover, three studies reported by Nawi et al., Lu et al., and Soliman et al., showed that there was a significant reduction in incidence of oral mucositis in the intervention group compared to the control group. Rodrigues et al., reported that cryotherapy proved effective in the intervention group to reduce the incidence of oral mucositis, between the first and second assessments ($p=0.000126$).[14,16,21] Johansson et al., reported that 2-hours cryotherapy was as effective as 7-hours cryotherapy in preventing oral mucositis in myeloma patients treated with high-dose melphalan.[22]

The assessment of oral mucositis severity was using standard instruments to measure grade and pain of oral mucositis. Six studies reported that the severity of oral mucositis was reduced in the intervention group. Mishra et al., reported that there was a reduction in severity of oral mucositis in the group given flavored ice cubes (honey and tulsi) compared to water ice cubes on day 5 and day 15 ($p = 0.001$).[20] Nawi et al., and Soliman et al., reported a significant reduction in pain in the intervention group.[14.16]

On the other hand, Kamsvåget et al., reported that oral cryotherapy did not reduce the incidence and severity of oral mucositis. Kamsvåget et al., found no difference between children in the intervention group and the control group regarding the level of mucositis scores (ChIMES). Oral mucositis was noted in 39 children (80%) and severe oral mucositis in 26 children (15 and 11 children in the intervention and control groups, respectively).[17]

DISCUSSION

Oral mucositis is a side effect of cancer therapy in the form of chemotherapy, radiotherapy and chemoradiotherapy. Oral mucositis due to chemotherapy or radiotherapy has similar clinical features, such as erythematous, ulcerated and painful.[1,2,4–6,8,10,13,23,24] The pathogenesis of oral mucositis is triggered by chemotherapy and radiation which is directly injure DNA, subsequently the chain is broken and causes basal epithelial cell death.[1,5,6,8,15] Severe oral mucositis is characterized by ulcerative lesions on the mucosa of the soft palate, lateral tongue, buccal mucosa, tonsils and severe pain that makes it difficult to eat.[4,8,15] If the functional impairment due to oral mucositis is not treated, it will decrease the patient's quality of life.[6.12]

Cryotherapy or cold therapy is a method of treating injuries using ice.[24] The history of cryotherapy was introduced by an English doctor named Arnott in 1851.[25] Oral cryotherapy by sucking ice cubes is an effective non-pharmacological therapy to prevent and reduce the severity of oral mucositis. Conventional oral cryotherapy techniques are easy to perform, inexpensive, generally well tolerated by patients and do not cause side-effects.

Table 1 Assessment of the research methods quality using the Modified Jadad Scale[19]

Reference	Question number								Total Score	Result
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)		Article quality
Mishra et al.	1	1	0	0	1	1	0	1	5	High
Nawi et al.	1	1	0	0	0	1	0	1	4	High
Johansson et al.	1	1	0	0	0	1	0	1	4	High
Lu et al.	1	1	0	0	1	1	0	1	5	High
Soliman et al.	1	1	0.5	0	0	1	0	1	4.5	High
Kamsvåg et al.	1	1	0	-1	1	1	0	1	4	High
Rodrigues et al.	1	1	1	1	1	1	0	1	7	High

Table 2 Population information, sample size, type of cancer, cancer therapy and intervention

Author, Country	Sample (N)	Type Cancer	Cancer Therapy	Types of Ice
Mishra et al. (2017), India	Control group=20 Intervention group=20	Hematologic *cancer*	fluorouracil and methotrexate	Water ice cubes Ice cubes made from tulsi & honey
Nawi et al. (2018), Malaysia	Control group=44 Intervention group=44	Colorectal cancer	fluorouracil	Water ice cubes
Johanson et al. (2019), Sweden	Control group=48 Intervention group=46	Multiple Myeloma	Chemotherapy (high-dose dose Melphalan) & autologous stem cell transplantation	Water ice cubes
Lu et al. (2019), China	Control group=35 Intervention group= 110	Hematologic *cancer*	HSCT with busulfan-cyclophosphamid	Water ice cubes
Soliman et al. (2019), Egypt	Control group=20 Intervention group=20	Gastric or Colorectal cancer	chemotherapy with Fluorouracil and Leucovorin	Water ice cubes
Kamsvåg et al. (2019), Sweden	Control group=27 Intervention group=26	Hematologic *cancer*	HSCT	Water ice cubes
Rodrigues et al. (2020), Brazil	Control group=30 Intervention group=30	Gastro-intestinal tract cancer	chemotherapy with 5-fluorouracil and Leucovorin	Water ice cubes

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Table 3 General summary of the reviewed article

Author	Assessment instrument	Interventions/Experiments	Comparison/ Control	Parameters and results	*Outcome*
Mishra *et at.*(2017)	WHO mucositis scale	Sucking flavored ice cubes (honey and tulsi), 5 minutes before chemotherapy and 25 minutes during chemotherapy.	Sucking water ice cubes, 5 minutes before chemotherapy and 25 minutes during chemotherapy.	1.Incidence of oral mucositis Day 5: 40% in the intervention group; 90% in the control group. Day 15: 15% in the intervention group; 80% in the control group. 2.Severity of oral mucositis Day 5: 0 patient had severe oral mucositis in the intervention group; 5 patients had severe oral mucositis in the control group. Day 15: 0 patient had severe oral mucositis in the intervention group; 0 patient had severe oral mucositis in the control group.	Flavored ice cubes (honey and basil) > water ice cubes
Nawi et al. (2018)	1. WHO mucositis scale 2. Visual analog pain scale (VAS)	Sucking ice cubes for 30 minutes during chemotherapy	No ice	1. Incidence of oral mucositis. 11 patients in the intervention group; 39 patients had oral mucositis in the control group. 2. Oral mucositis pain. 13 patients had mild pain in the intervention group; 38 patients had moderate-severe pain in the control group.	Ice cubes > no ice cubes
Johansson et al. (2019)	1. WHO mucositis scale 2. OMAS mucositis scale 3. Incidence & duration of total parenteral nutrition 4. Incidence of use of opioid analgesics 5. Incidence of bacteremia and fever 6. Hospitalization duration	Sucking ice cubes for 2 hours during chemotherapy	Sucking ice cubes for 7 hours during chemotherapy	1. There was no significant difference between the two groups based on the WHO and OMAS mucositis scales. 2. There were no significant differences between the two groups based on hematological toxicity, infection, analgesic requirements and total parenteral nutrition.	Ice cubes for 2 hours = ice cubes for 7 hours
Lu et al. (2019)	Oral mucositis scale: NCI-CTC (National Cancer Institute Common Toxicity Criteria)	A: cryotherapy from early to late conditioning B: cryotherapy from mid-late conditioning C: cryotherapy 2 times a day during the conditioning period	D: The patient is instructed to maintain oral and dental hygiene without cryotherapy	1. Incidence of oral mucositis *Grade* 3-4: group A 5 people, group B 7 people, group C 15 people, group D 15 people 2. Duration and recovery time of oral mucositis The duration of oral mucositis in the A&B group was 2 days, the C&D group was 7 days. The shortest recovery time for oral mucositis in the A&B group was 6-7 days, in the C&D group, which was 8-10 days.	Ice cubes > no ice cubes
Soliman et al. (2019)	1. WHO mucositis scale 2. *NRSI* (Numerical Rating Scale for Pain Intensity)	The patient sucked ice cubes 5 minutes before, during chemo-therapy & 5 min. after chemo-therapy, total time 20-25 min,	Patients applied standard oral care without cryotherapy	1. Incidence of oral mucositis. Free from oral mucositis in the intervention group 45% and in the control group 0%. 2. Oral mucositis pain. Free from oral mucositis pain in the intervention group 40% and in the control group 0%.	Ice cubes > no ice cubes
Kamsvåg et al. (2019)	1. WHO mucositis scale 2. ChIMES/Children's International Mucositis Evaluation Scale 3. NRS (Numerical Rating Scale)	Patients sucked ice cubes during chemotherapy for at least 30 minutes.	Received standard oral care without cryotherapy	Incidence & pain of oral mucositis There was no difference between children in the intervention group and the control group regarding grade of oral mucositis.	Ice cubes = no ice cubes
Rodrigues et al. (2020)	WHO mucositis scale	Sucking ice cubes in the oral cavity started 5 minutes before chemotherapy & 30 minutes during chemotherapy.	Gargle with 10 mL of physiological solution for 1 minute, 3x/day for 14 days after chemotherapy.	Incidence and severity of oral mucositis: The reduction in oral mucositis in the experimental group (intraclassical analysis), between the first and second assessments, was statistically significant (p=0.000126).	Ice cubes > saline

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Mishra et al., Nawi et al., Johansson et al., Lu et al., Soliman et al., and Rodrigues et al., stated that sucking ice cubes can reduce the incidence and severity of oral mucositis significantly.[14,16,20–22,26] The mechanism of cryotherapy produce local vasoconstriction by cold temperature, thereby limiting exposure of chemotherapy drugs to the oral tissue.[2,27] If the exposure of chemotherapy drugs to the oral mucosa is reduced, the mucocosal tissue damage can be minimized.[27]

In addition, Nawi et al., and Soliman et al., showed that sucking ice cubes can reduce the pain of oral mucositis.[14.16] The cold temperature from ice cubes causes microvascular changes that decrease the production of inflammatory mediators, minimize local edema and reduce nerve conduction velocity.[28] Ice cubes can freeze nerve tissue, thereby changing ischemic conditions and reducing energy to conduct stimuli.[25] Undoubtedly, sucking ice cubes provide a calming effect.[8]

The application of ice cubes for oral mucositis by sucking ice cubes in the mouth cavity 5-30 minutes,[15] even for 2-7 hours in a study conducted by Johanson et al.[22] If the ice melts and dissolves, the patient is expected to suck a new ice cubes immediately. The size of the ice cubes used is not absolute, but in a study conducted by Lu et al., the ice cubes used were 3 cm x 3 cm x 1 cm. The shape of the ice cube should be round, thereby it does not irritate the oral mucosa and the patient swallow easily.[21] The principle of sucking ice cubes for oral mucositis must prioritize patient's comfort and could be tolerated by the patient.[25]

Furthermore, Mishra et al., investigate the effectiveness of oral cryotherapy using flavored ice cubes which are a combination of natural product and herbal medicine (honey and tulsi).[20] The results of this study indicate that oral cryotherapy using flavored ice cubes can reduce the occurrence of oral mucositis significantly compared to water ice cubes. This study is intended to take advantage of honey and tulsi. Honey has antibacterial, antifungal and anti-inflammatory effects and helps in re-epithelialization.[8,30] Tulsi has been studied pharmacologically to have antimicrobial, immunomodulatory, anti-inflammatory and analgesic effects.[31]

On the other hand, in the results of a study conductducted on pediatric patients by Kamsvåg et al., it was concluded that sucking ice cubes was not effective to reduce the incidence and severity of oral mucositis. The study explained that the possible cause of the ineffective ice cubes in oral mucositis was the low level of children's adherence to intervention instructions, especially in children under 4 years old.[17]

Singularly, there is one study that could be developed for further research, the combination of cryotherapy with other active ingredients such as honey, tulsi, or other herbal medicine. It is intended to obtain a synergistic effect to accelerate the healing of oral mucositis. Moreover, the use of flavored ice cubes with combinations such as honey, milk and fruit may increase children's adherence to the study intervention. The limitations of this systematic review may be that there are articles that are in accordance with the research objectives but could not be identified in the database used, or the complete manuscript is not available. This systematic review could be an important information base for further research in the field of oral disease.

It is concluded that oral cryotherapy by sucking ice cubes has proven to be effective in preventing and reducing the severity of oral mucositis so that it can improve the quality of life in patients undergoing cancer therapy. The cold sensation of ice cubes causes local vasoconstriction, reduces pain, and prevents swelling.

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