Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2021 Nov 30; 9(F):650-659.
https://doi.org/10.3889/oamjms.2021.7712
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Systematic Review Article*

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Effectiveness of Oral Cryotherapy for Oral Mucositis on Cancer Patient Undergoing Cancer Therapy: A Systematic Review

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Edited by: Eli Djulejic
Citation: Erika KA, Mulhaeriah M, Miskad UA, Zuraida E, Achmad H. Effectiveness of Oral Cryotherapy for Oral Mucositis on Cancer Patient Undergoing Cancer Therapy: A Systematic Review. Open Access Maced J Med Sci. 2021 Nov 30; 9(F):650-659. https://doi.org/10.3889/oamjms.2021.7712
Keywords: Cryotherapy; Oral mucositis; Cooling therapy; Cancer; Cancer therapy
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Received: 26-Oct-2021
Revised: 12-Nov-2021
Accepted: 24-Nov-2021

Funding: This study was supported by DRPM KEMENRISTEK-BRIN Funding for 2020
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Oral mucositis is one of the complications in patients undergoing cancer therapy. Oral cryotherapy (OC) is an intervention to reduce the severity of oral mucositis.

AIM: To identify, analyze, and evaluate articles regarding the effectiveness of cryotherapy for oral mucositis in cancer patients undergoing cancer therapy.

METHODS: We performed searching on seven databases (PubMed, CENTRAL, Wiley, CANCERLIT, Science Direct, EBSCO, and SpringerLink). The investigation focused on English-language articles, intervention, or observational study reporting on the effectiveness of OC against oral mucositis in patients undergoing chemotherapy, and published between October 2015 and October 2020.

RESULTS: Eleven articles met the eligibility criteria for inclusion consisting of 5 RCTs, 3 Quasi-Experiment studies, 2 Cohort studies, and one pre-experimental study. The majority of the studies show that OC is an effective intervention to reduce the degree and severity of oral mucositis in patients undergoing cancer therapy (Hematopoietic Stem Cell Transplantation and chemotherapy).

CONCLUSION: OC is practical, low-cost, and relatively safe and can be an alternative therapy in reducing oral mucositis as a side effect of cancer therapy.

Introduction

Cancer is projected as the top rank among the majority of diseases that have caused the highest incidence of death in the world. Global Burden Cancer notes that the million cases in 2018 [1]. In the United States, an estimated 1.8 million new cancer cases, with a death rate of more than 600 thousand cases by 2020 [2]. The prevalence of the cases demands the implementation of cancer therapy which can prolong survival and improve patient quality of life.

At present, combined cancer therapies for example surgery, chemotherapy, and radiotherapy have shown promising results on patient's survival; however, the cancer therapy can also cause side effects which affect the patient's quality of life [3]. One of the most common side effects of cancer therapy is oral mucositis [4], [5], which were experienced by 20–80% of patients receiving chemotherapy, 73.2% of patients undergoing Hematopoietic Stem Cell Transplantation (HSCT) [6], and by almost all patients that receive radiation therapy in the head and neck area [7].

Oral mucositis is characterized by inflammation and damage to the mucous membrane of the mouth [8]. Oral mucositis conditions can cause pain in the mouth, decreased/changed sense of taste, dry mouth, decreased saliva production, difficulty swallowing, decreased food intake, and secondary infections [9], [10]. This condition can have a negative physical and psychological impact on the quality of life of cancer patients [11]. Thus, prevention and treatment of oral mucositis as a result of cancer therapy requires appropriate intervention.

Complementary and alternative medicine therapies have been used by patients to treat various symptoms [12]. One of them is oral cryotherapy (OC) for managing oral mucositis is cryotherapy [13], [14]. OC is the application of ice chips before, during and after therapy which is useful in preventing and relieving oral mucositis [15], [16]. This intervention is easy to be applied and causes no severe side effects [14].

There are several studies that have been conducted to evaluate cryotherapy as treatment and prevention risk of oral mucositis; more focused on kind of cancer treatment [17], [18], [19]. However, there

is limited studies that discussed tools to determine level of mucositis, how to apply this intervention, and effectiveness of cryotherapy itself, not only for oral mucositis, but also for another side effect of cancer therapy. Therefore, this study aimed to systematically identify, analyze, and evaluate articles regarding the effectiveness of OC to oral mucositis in cancer patients undergoing cancer therapy, focusing on assessment of mucositis, procedure, and effectiveness of an intervention.

Methods

This study is a systematic review. We refer to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist-guideline [20], in assessing and evaluating the studies in this review. We can freely be assessed in http://www.prisma-statement.org/.

Search strategy

Literature searches were conducted from September 15 to October 23, 2020, on seven databases: PubMed, CENTRAL, Wiley, CANCERLIT, Science Direct, EBSCO, and SpringerLink. Patient, intervention, comparison, and outcome (PICO) framework was used to facilitate the search strategy, for instance, P: Cancer OR neoplasms, I: Cryotherapy OR cooling therapy, C: No comparison, and O: Oral mucositis. PICO and the usage of the keywords depend on the database, which was combined with the use of Boolean "AND" and "OR" (Table 1). In addition, we also searched for articles outside the databases as a secondary search, namely, on Google Scholar.

Eligibility criteria

Studies were included in this review if they met the following criteria: 1) Articles published in English; 2) intervention or observational studies; 3) articles reporting on the effectiveness of cryotherapy on oral mucositis experienced by cancer patients undergoing cancer therapy; and 4) articles published from October 2015 to October 2020. Review articles, editorial reviews, qualitative studies, abstracts, and conference proceedings were excluded from the study.

Study selection

Titles and abstracts were screened based on predetermined inclusion and exclusion criteria. Furthermore, we held panel discussion until an agreement was reached in determining which articles were suitable for inclusion in this study. There were 1687 articles identified in the database, and ten articles on secondary searches outside the databases. Subsequently, papers that had duplicates were excluded from the study, so that 1564 articles were obtained. Subsequent screening eliminated 1475 items and finally only 89 articles remained for assessment (5.69%). We assessed the full-text articles to determine the eligibility of the studies. After the consensus of the review team, we excluded 78 articles and only 11 studies meet eligibility criteria for this review (Table 1). The study inclusion process is illustrated in a PRISMA flow chart (Figure 1).

Evaluation of quality of articles

We used the Critical Appraisal Skills Program tools [21], [22], to assess the feasibility of the included studies (Table 2).

Table 1: Search strategy of electronic databases

Database	Search terms	Result	Search screening	Screening result	Include studies
PubMed	((((((Cancer[MeSH Terms]) OR (neoplasms[MeSH Terms])) AND (cryotherapy[MeSH Terms])) OR (cryotherapies[MeSH Terms])) OR (cold therapy[MeSH Terms])) OR (cold therapies[MeSH Terms])) AND (oral mucositis[MeSH Terms])	88	5 years: 26 Full text: 25	25	4
CENTRAL	Cancer in Title Abstract Keyword OR neoplasms in Title Abstract Keyword AND cryotherapy in Title Abstract Keyword OR cooling therapy in Title Abstract Keyword AND oral mucositis in Title Abstract Keyword - -	156442	2016-2020: 58474 1000 articles most relevant: 22	22	1
Wiley	"Cancer" in Abstract and "chemotherapy OR radiotherapy" in Abstract and " OC " in Abstract and "oral mucositis" in Abstract	13	Last 5 Years: 3	3	0
CANCERLIT	Cancer OR neoplasm AND cryotherapy OR cooling therapy AND oral mucositis	102	Last 5 years: 50 English: 49	49	1
Science Direct	Cancer OR neoplasms AND cryotherapy OR cryotherapies OR cooling therapy OR cooling therapies AND oral mucositis title: mucositis	8618	2016–2020: 1721 Research article: 828	828	0
EBSCO	Cancer OR neoplasm AND (cryotherapy or ice therapy or cold therapy) AND oral mucositis	6235	5 years: 946 Academic Journals: 639	639	0
SpringerLink	Cancer OR neoplasms AND cryotherapy OR cooling therapy AND oral mucositis.	571	2016–2020:221 Articles: 111	111	0
Secondary Search outside of the database				10	5
Total include studies					11

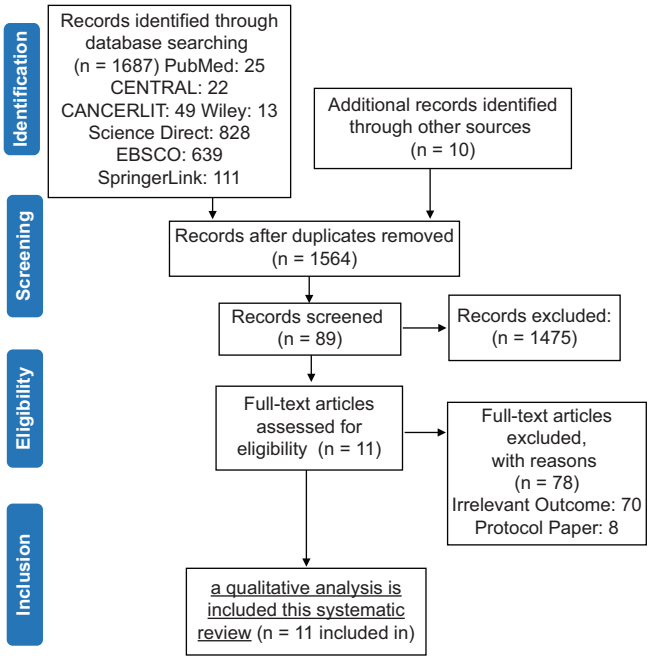

Figure 1. PRISMA Flow Chart

Data extraction

Data extraction process was carried out and developed in the form of a synthesis grid (Table 3). The data includes researcher, year, study design, objective, type of cancer, mucositis assessment, outcome measurement, OC procedures, and research results. The accuracy of data extraction is ensured by checking the data 3 times by reviewer panels.

Results

Assessment of oral mucositis

Eleven studies included in this review used different instruments to assess oral mucositis in cancer patients undergoing cancer therapy. The instruments were the WHO mucositis scale [23], [28], [30], [31], [33], the Oral Assessment Guide (OAG) [27], [29], the Oral Mucositis Assessment Scale (OMAS) [23], the National Cancer Institute Common Toxicity Criteria (NCI-CTC) [24], and Oral Mucositis Daily Questionnaire (OMDQ) [24], [26]. The OMDQ is a self-assessed questionnaire, whereas other tools are used by health practitioners. However, there are two studies that did not specifically mention the instrument used to assess the oral mucositis in their studies.

OC procedure

Several studies have shown the time to assess the degree of mucositis in cancer patients receiving cancer therapy, but it is still varied. The principle of applying ice cube into the mouth as a core part of the

Table 2: Critical appraisal

S. No.	Appraisal checklist experimental studies	Johansson *et al.* (2019)	Lu *et al.* (2019)	Nawi *et al.* (2018)	Askarifar *et al.* (2016)	Soliman (2019)	Silaban *et al.* (2020)	Parajuli *et al.* (2016)	Turkeli *et al.* (2017)	Bai (2019)	S. No.	Appraisal checklist cohort studies	Okamoto *et al.* (2019)	Chen *et al.* (2015)
1.	Focused issue	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.	Focused issue	Y	Y
2.	Randomization	Y	Y	Y	Y	Y	N	Y	N	N	2.	Recruited in an acceptable way	Y	Y
3.	All of the patients properly accounted for at its conclusion	Y	Y	Y	Y	Y	Y	?	?	N	3.	Exposure accurately measured	Y	Y
4.	Blind	N	?	N	Y	?	?	?	?	N	4.	Outcome accurately measured	Y	Y
5.	The groups similar at the start of the trial	Y	Y	Y	Y	Y	Y	Y	Y	N	5.	Identified all-important confounding factors	?	N
6.	The groups treated equally	Y	Y	Y	Y	Y	Y	Y	Y	Y	6.	The follow up of subjects complete and long enough	Y	Y
7.	Intervention effect accounted	Y	Y	Y	Y	Y	Y	?	Y	N	7.	Reported the rate or the proportion between the exposed/ unexposed, the ratio/rate difference	?	N
8.	The accuracy of the estimated effect of the intervention can be accounted	Y	Y	?	Y	Y	Y	?	?	?	8.	How precise are the results	Y	Y
9.	the results can be applied to the local population, or in your context	?	?	Y	?	Y	Y	?	?	?	9.	Believe the results	Y	Y
10.	All clinically important outcomes were considered	Y	Y	Y	Y	Y	Y	?	Y	?	10.	Can the results be applied to the local population	Y	Y
11.	Are the benefits worth the harms and costs	?	Y	?	Y	?	Y	?	Y	?	11.	Fit with other available evidence	Y	Y
											12.	The implication of nursing practice	Y	Y
	Level of evidence	1c	1b	2b	1b	2b	2b	2c	2b	2c		Level of evidence	2b	2b
	Grade of recommendation	A	A	B	A	B	B	B	B	C		Grade of recommendation	B	B

Y: Yes, N: No, ?: Can't Tell

Tabel 3: Synthesis grid

Researcher; country	Design study	Aim	Type cancer	Cancer therapy	Assessment mucositis	Another outcome measurement	Procedure OC	Result
Johansson *et al*. (2019); Sweden [23]	RCT	To investigate whether 2 h of cryotherapy is as useful as 7 h of cryotherapy in treating oral mucositis in patients receiving high doses of Melphalan as auto SCT in myeloma patients	Multiple Myeloma	Chemotherapy (high-dose Melphalan) and autologous stem cell transplantation	WHO and OMAS scale	Infectious haematological toxicity Analgesic needs TPN	Ice cube is given 30 min before the drug is given. The patient did not take any other oral intake during cryotherapy and were instructed to melt about one tablespoon of shaved ice in their mouth and immediately replenished. Duration: 2 h and 7 h of cryotherapy The oral mucositis assessment was performed before cryotherapy (day 2), just before stem cell infusion (day 0), and every day it was started+4 days until the resolution of the mucositis.	Primary Outcome: No significant difference was observed in reference to the proportion of patients presenting with grade 3 and 4 toxicity according to the WHO Scale (2.1 and 4.3% over 2 and 7 h, respectively; 95% CI: −0.09–0.049; *P* = 0.98) between the two groups. Secondary Outcome: There is no significant difference between IC and CG regarding haematological, infectious and toxicity need for analgesics and TPN.
Lu *et al*. (2019); China [24]	RCT	To determine the best time to administer OC to prevent oral mucositis in patients undergoing HSCT	Hematology Cancer	HSCT	NCI-CTC version 2 OMDQ	Duration and recovery time for severe oral mucositis	Patients were given an ice cube with a round angle, measuring (3.2 cm×3.3 cm× 1 cm), comparing the administration of ice cube to 3 groups who received OC intervention, some were given early initiation of therapy, in the middle, and administration of ice cube 15 min 2 times a day. Patients can have a pause of 60-180 seconds if they feel uncomfortable. Mucositis assessments were carried out daily for up to 15 days after the completion of HSCT	Primary Outcome: Both groups of patients who were given OC before and at the time of receiving HSCT had a low incidence of mucositis and a short duration of mucositis (≥ level 3), although there was no significant difference. The incidence of mucositis was highest in the group given OC after the HSCT procedure. Secondary Outcome: OC administration can reduce the duration and recovery time of severe mucositis
Okamoto *et al*. (2019); Japan [25]	Retrospective cohort study	Evaluating the role of OC as a prophylaxis in patients receiving DCF therapy	Esophageal Cancer	Chemotherapy (DCF)	Grading Oral mucositis, but it was not mentioned what kind of assessment	Anorexia level	Ice cube is given to patients 10 min before DCF is given until the completion of therapy. The total water content in the ice provided is 200–300 ml. The chunks of ice are round on each side.	Primary Outcome: The Incidence of oral mucositis in all grades and grade 3 was significantly lower in the OC group than in the non-OC group than in the non OC-group (24.1% vs. 71.4%, *P* < 0.001 and 0% vs. 28.6%, *P* = 0.001 respectively) Secondary Outcome: The incidence of anorexia in all grades and grade 3 was significantly lower in the OC group (22.4% vs. 57.1%, *P* = 0.037 and 0% vs. 28.6%, *P* = 0.010, respectively)
Nawi *et al*. (2018); Malaysia [26]	RCT	Evaluating the effectiveness of oral mucositis in the prevention of oral mucositis and pain in colorectal cancer patients undergoing fluorouracil chemotherapy	Colorectal Cancer	Chemotherapy	WHO Mucositis Scale	Pain associated OM with VAS scale	Giving ice chips for 30 min while the chemo drug is given	Primary Outcome: The majority of CG participants exhibited grade 2 mucositis levels and more significant grading compared to IG (p = < 0.001). Secondary Outcome: The majority of participants in IC reported no pain

(*Contd*...)

Tabel 3: (*Continued*)

Researcher; country	Design study	Aim	Type cancer	Cancer therapy	Assessment mucositis	Another outcome measurement	Procedure OC	Result
Silaban *et al*. (2020); Indonesia [27]	Quasi-experiment	To identify the effectiveness of OC in the prevention of oral mucositis in cancer patients undergoing chemotherapy	Solid Cancer	Chemotherapy	OAG	-	There is no specific mention of the OC procedure. However, it is described that the oral mucositis assessment was performed at 7 and 14 days after the intervention	Primary Outcome: There is a difference in the value of mucositis after being given OC treatment (post) where 29 respondents did not experience mucositis, and three respondents experienced mucositis. While in CG, 18 respondents experienced mucositis and did not experience mucositis 12. The degree of mucositis of patients in the two treatment groups was found to be significant.
Parajuli *et al*. (2016); India [28]	Quasi-experiment	To evaluate the effectiveness of OC in treating oral mucositis experienced by patients undergoing chemotherapy	All-type cancer	Chemotherapy	WHO Mucositis Scale	-	Ice cubes were given to IG for 5 days, 5 min before, two times during chemo, and 5 min after chemotherapy. Patients in both treatment groups had Grade I and Grade II mucositis.	Primary Outcome: There was a decrease in the degree of mucositis of patients who were given OC compared to those who did not get OC
Bai (2019); India [29]	Pre-experiment study	To assess the degree of oral mucositis of patients receiving chemotherapy before and after OC	Solid Cancer	Chemotherapy	OAG	-	Ice cubes were applied to the oral mucosa for 5 min before the chemotherapy session and 20 min after the session. The post-test assessment using OAG was carried out on the 7th day.	Primary Outcome: There was a significant difference between the pre-test and post-test scores of oral mucositis levels among cancer patients receiving chemotherapy. Secondary Outcome: OC was significantly effective in reducing the degree of oral mucositis in patients receiving chemotherapy. There is a significant relationship between the degree of oral mucositis after OC in patients receiving chemotherapy with demographic variables such as age, gender, religion, educational status, marital status, and causes of disease
Askarifar *et al*. (2016); Iran [30]	RCT	To determine the effectiveness of OC in patients who receive continuous chemotherapy with oral mucositis while undergoing bone marrow transplantation	Multiple Myeloma, Hodgkin's dan Non-Hodgkin's Cancer	Chemotherapy	WHO Mucositis Scale	Neutrophil Rate	Ice cubes were applied 5 min before, during, and after each dose of chemotherapy drug. Initially, ice cubes were used continuously, once, for 30 min. Then, with a maximum break of 20 min, ice use is restarted for the next 30 min and continues up to 5 min after the completion of chemotherapy. However, a hot sensation in the mouth of fewer than 20 min is considered a factor in reusing ice. Ice cubes as ice moulds measured approximately three by four centimeters in a sterile container were prepared for the patients. Mucositis assessments were carried out on days 3, 7, 14, and 21 after chemotherapy	Primary Outcome: OC was more effective than normal saline in reducing the severity of mucositis in patients receiving chemotherapy (1.81<2.54 and 0.13<0.92, respectively) on days 7 and 14 ($p < 0.164$) Secondary Outcome: There was no difference in neutrophil values in the two treatment groups.

(*Contd*...)

Tabel 3: (*Continued*)

Researcher; country	Design study	Aim	Type cancer	Cancer therapy	Assessment mucositis	Another outcome measurement	Procedure OC	Result
Soliman (2019); Egypt [31]	RCT	To determine the effectiveness of cryotherapy in dealing with the severity of oral mucositis caused by chemotherapy and pain due to oral mucositis in patients receiving combination chemotherapy (Fluorouracil and Leucovorin).	Gastrointestinal Cancer	Chemotherapy	WHO Mucositis Scale	The pain was assessed with the NRS	Ice cubes are given 5 min before, during chemo, and 5 min after chemotherapy, a total time of 20–25 min. If the ice cubes melt, they must be replaced immediately. If the patient is uncomfortable with ice cubes in the mouth, he can rest for no more than 30 min. The ice cubes used have round corners. The ice used must be the right size and can be moved in the mouth. Mucositis assessment was carried out on day 7, 14, and 21 days	Primary Outcome: In the majority of patients in the cryotherapy group, oral mucositis was undetectable (Grade 0) on days 7, 14, and 21. The incidence of similar grade 1 and Grade 2 oral mucositis in the cryotherapy group was significantly reduced when compared with the control group where $P < 0.001$. Secondary Outcome: patients in CG showed a significantly higher level of oral discomfort (p = 0.001).
Turkeli *et al*. (2016); Turkey [32]	Quasi Experiment	To determine whether cryotherapy can prevent mucositis caused by 5-FU therapy through oral mucosal smears by looking at cytological changes	Gastrointestinal Cancer	Chemotherapy	Grading Oral mucositis but did not mentioned kind of assessment	Exfoliative cytology of oral mucosal swabs	Patients were instructed to apply it in the oral cavity 5 min before, 5 min during, and 30 min after the 5-FU drug administration. Assessment of mucositis was started on day one and day 14 of chemotherapy	Primary Outcome: The nuclear and cytoplasmic volumes in cells decreased significantly in patients receiving cryotherapy compared to pre-cryotherapy (0.047 and 0.042, respectively). The results of the histomorphometry estimation show that cryotherapy can be used to prevent oral tissue damage and can reduce the frequency and duration of oral mucositis caused by 5-FU. Secondary Outcome: Grade I and II mucositis decreased significantly in patients receiving cryotherapy compared to patients without cryotherapy (p = 0.03)
Chen *et al*. (2015); Canada [33]	Retrospective cohort study	to examine the effectiveness of the cryotherapy protocol applied in a hematopoietic stem cell transplant program.	Multiple Myoma	HSCT	WHO mucositis scale	Duration of oral mucositis, length of stay in the hospital, use of narcotics and use of total parenteral nutrition.	The patient is instructed to hold the ice flakes inside mouth for 5 min before high-dose melphalan infusion, for 30 min and 30 min after completion of the infusion.	Primary Outcome: The incidence and severity of mucositis were found to be significantly lower in the cryotherapy group. 71.4% had mucositis in the OC group compared with 95.7% in CG (p < 0.001). The median mucositis severity, assessed using the WHO oral toxicity scale from 0 to 4 levels, experienced in CG was 2.5 versus 2 in the OC group (p = 0.03). Secondary Outcome: The duration of oral mucositis and use of parenteral narcotics was also significantly reduced. Duration of hospitalization and use of parenteral nutrition were similar between the two groups.

5-FU: 5-fluorouracil, DCF: Docetaxel, cisplatin, and fluorouracil; CG: Control group; HSCT: Haematopoietic stem cell transplantation; IG: Intervention group; NRS: Numeric rating scale; OAG: Oral assessment guide; OC: Oral cryotherapy, OMAS: Oral mucositis assessment score, OMDQ: Oral mucositis daily questionnaire; RCT: Randomized control trial, TPN: Total parenteral nutrition, VAS: Visual analogue scale, WHO: World health organization

cryotherapy procedure was relatively similar among the reviewed studies. However, there was a slight difference in the time of administration. The majority of studies applied OC procedures before cancer therapy

interventions were carried out. Six studies started giving ice cube 5 min before cancer therapy was started [28], [29], [30], [31], [32], [33]. Another study started 10 min [25] and 30 min before cancer therapy was given [23].

Beside time of OC application, duration during therapy was also varied. Some studies started OC when the treatment was begun; mid until the treatment is finished with a period ranging from 5 to 30 min, and some even reach 2–7 h, some are once or twice. Some are continuous until the therapy is completed, followed by a pause if the patient experiences inconveniences. The majority of the research evaluated the degree of mucositis 1–2 weeks after the intervention.

Regarding the size of the ice cube, only four studies that describe the ice cube criteria were used for the OC [24], [25], [30], [31]. In detail, Lu *et al*. stated that the size of the ice cube was 3.2 cm × 3.3 cm × 1 cm [24]. Another study describes that the ice cube made from ice molds measuring three by four centimeters in a sterile container [30]. Okamoto *et al*. further explained the total water content for making ice cube, which was around 200–300 mL for making ice chunks [25]. Meanwhile, Soliman *et al*. did not explain size details, but the criteria for the ice cube must be suitable and moveable in the mouth [31]. Although the size criteria of the ice cube were different, these studies agreed that the ice cube used were rounded corners to prevent mouth irritation.

The effectiveness of OC to oral mucositis in patients undergoing cancer therapy

The majority of the reviewed studies described that OC intervention was effective in reducing the degree and severity of oral mucositis in patients undergoing cancer therapy, either HSCT or chemotherapy. Based on the mucositis grading assessment instruments, these studies found mucositis grade reduction in the OC group [25], [26], [27], [28], [29], [30], [31], [32]. Meanwhile, three studies reported that the incidence of oral mucositis on different grades was significantly lower in the group of patients receiving OC than the non-OC group [25], [26], [31].

Similar results were also found in patients who underwent HSCT in which the severity of mucositis was significantly lower in the group receiving OC [30], [33]. Additional studies conducted by Lu *et al*. found that patients who were given OC before and while receiving HSCT had a lower incidence of mucositis or a short duration of mucositis (≥ level 3), although there was no significant difference statistically [24].

The effectiveness of OC on other outcomes in patients undergoing cancer therapy

Ten other outcomes were assessed regarding the effectiveness of OC. It was found that the OC decreased pain level of the patients oral mucositis [26], [31], shorter the duration and recovery of severe mucositis [24], [33], reduced the incidence of anorexia [25], and usage of parenteral narcotics [33]. Furthermore, the exfoliative cytology results on the oral mucosal layer showed a decrease in the nuclear and cytoplasmic volume in cells after the OC [32]. However, there were no significant differences between OC and controlled groups in term of the level of toxicity of infectious hematology, analgesic need, TPN [23], the neutrophil rate [30], and length of hospitalization [33].

Discussion

We conducted a review on relevant studies, to assess the effectiveness of OC for oral mucositis on cancer patient undergoing cancer therapy. This review focuses on the assessment of oral mucositis, the OC procedure, and the effectiveness of the OC. Assessment of the degree of patient mucositis is an essential component in evaluating the effectiveness of the OC intervention. This review found several instruments used in the included studies.

This diversity of instruments is a clinical-based assessment tool that can be used to assess signs of oral mucositis. The OMDQ is a self-reported instrument that can be an alternative clinical assessment if the patient refuses to do an oral examination by health practitioners [34]. A research conducted by Wardill *et al*. reported that the NCI-CTC is an instrument that is more widely used in assessing oral mucositis in cancer patients, followed by the Radiation Oncology Research Group, the WHO mucositis scale, OMAS, Oral Mucositis Index, and OAG [35]. This research does not specify which one is the most effective instrument and more emphasize the importance of using a validated instrument in assessing mucositis. The usage of the tool must follow the principles of validity and must be able to assist in determining the degree of mucositis so that the appropriate treatment can be applied. In addition, in assessing the degree of mucositis, two instruments can be combined, such as assessment instruments from health practitioners and self-reported instruments.

The OC implementation protocol in each of the reviewed studies have a relatively same regarding the application principle, but difference in the procedural time and duration. Previous research, in patients undergoing chemotherapy, Ameen *et al*. stated that ice cube administration was given 10 min before therapy, continued 15 min each while treatment was taking place and after the chemotherapy infusion was complete [36]. Meanwhile, related to duration of OC administration, Research from Johanssen *et al*. proved that the duration of 2 h or 7 h of OC [23]. There was

no difference in results in determining the length of intervention in the treatment of oral mucositis.

The Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISO) also gave recommendations, not much different from the previous year's guidelines, it is stated that the recommended duration of OC administration is 30 min, because of more than 30 min can cause a sensation of discomfort [5], [37]. MASCC/ISO guidelines reveal that OC can be a modality to prevent oral mucositis in patients undergoing autologous HSCT accompanied by high doses of Melphalan, and in solid cancer patients receiving 5-FU therapy [37]. This means that the effectiveness of the duration of OC administration should take into account the patient's comfort during the procedure.

Regarding the size and volume of the ice cube/ice chip used, we have not found any definite size guidelines regarding its use and its effect on OC. From this review, we get a summary that the use of ice cube should prioritize patient comfort so that the ice cube used has rounded corners, is suitable and can be moved in the mouth.

In this systematic review, we found that OC can reduce the incidence and severity of oral mucositis in cancer patients undergoing cancer therapy. This review is in line with the management guidelines from MASCC/ISO [5], declared that OC is included as one of the palliative management of patients undergoing cancer therapy. OC is easy to apply, low cost, and relatively safe. OC is characterized by the use of an ice cube/ice chip which is readily available [31]. A study by Walladbegi *et al*. stated that the procedure was consistently lower the temperature in oral mucosa during the administration of cytotoxic drugs that can reduce the release of pro-inflammatory cytokines [38]. Thus, the effect of tissue damage can be minimized [38].

In addition, this review shows that OC is significantly shorter the pain level, duration and recovery of severe mucositis, a lower incidence of anorexia, decreased parenteral narcotic use, and decreased nuclear and cytoplasmic volume in the oral mucosal layer as a result of exfoliative cytology. Meanwhile, the toxicity level of infection hematology, analgesic requirement, neutrophil rate, length of stay and TPN were not significant. Ulceration of mucositis can cause pain [14]. However, through the cooling process in the oral cavity, it can cause a decrease in the release of inflammatory cytokines (IL-6 and TNF-α) [38], and reduce pain levels [39]. The pain decreases; the appetite increases so that the incidence of anorexia can be suppressed. OC can be a promising intervention in dealing with the side effects of cancer therapy.

Nurses can use the OC method as a nursing implementation in reducing oral mucositis in patients undergoing cancer therapy. Besides, nurses can use the grading mucositis assessment as a routine activity in evaluating the oral mucosa of cancer patients.

Conclusion

OC can be an intervention in preventing the incidence and reducing the degree and severity of oral mucositis in patients undergoing cancer therapy, either HSCT or chemotherapy. OC is practical, low-cost, and relatively safe to use. OC can be part of the management of oral mucositis by following appropriate procedural guidelines.

Acknowledgment

This work was supported by The Directorate of Research and Community Service – The Indonesian Ministry of Research, Technology and Higher Education, (Number: 1516/UN4.22/PT.01.03/2020). The authors would like to thanks to Moh. Syafar Sangkala for the suggestion in improving this manuscript.

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