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Effectiveness of cryotherapy in preventing oral mucositis in pediatric cancer patients in Jordan: a randomized controlled trial

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Purpose: The study aimed to evaluate the effectiveness of cryotherapy in preventing oral mucositis in pediatric patients receiving chemotherapy. **Methods:** An evidence-based practice project utilized a randomized control trial design with two groups (experimental and control groups). Fifty-nine pediatric patients with cancer in Jordan, aged 8–18 years, were randomly assigned to the experimental group (n=29) or the control group (n=30). The intervention was conducted from June 2022 to December 2022. The severity of oral mucositis among pediatric cancer patients was assessed using the World Health Organization oral mucositis grade. **Results:** There were no significant differences in sex or disease type among the groups. On days 7, 14, and 21, we observed notable between-group differences in treatment responses and the intensity of oral mucositis, highlighting the efficacy of cryotherapy in diminishing the severity of oral mucositis. **Conclusion:** This study supports the use of cryotherapy as a preventive measure for oral mucositis among pediatric oncology patients in Jordan. The findings suggest that cryotherapy effectively reduces the severity of oral mucositis. Further research is necessary to investigate the broader impacts of cryotherapy.

Keywords: Cryotherapy; Neoplasms; Pediatrics; Prevention and control; Stomatitis

INTRODUCTION

Oral mucositis, which is characterized by severe inflammation and sores in the mouth, commonly affects young cancer patients undergoing chemotherapy or radiation therapy [1]. This condition significantly impacts their quality of life and the effectiveness of treatment outcomes [2]. Addressing oral mucositis continues to be a significant challenge in pediatric oncology, as conventional treatments frequently fail to provide substantial relief [3].

Cryotherapy, which involves the application of cold therapy, has gained recognition as a potential method for both preventing and managing oral mucositis [4]. Applying cold temperatures to the oral cavity before, during, or after cancer treatments aims to reduce the severity and duration of mucositis symptoms [5,6]. Although cryotherapy has shown promising results in some studies, its effectiveness and the optimal protocols for use in pediatric cancer patients remain subjects of ongoing research.

This research is significant because it has the potential to improve the quality of life for pediatric cancer patients by reducing the frequency and severity of oral mucositis. As demonstrated by Correa et al. [5], cryotherapy has been recognized for its effectiveness in reducing the severity of mucositis, potentially enhancing patient comfort and adherence to treatment. Should cryotherapy be validated as an effective

preventive strategy, its integration into standard care protocols could significantly improve patient outcomes and minimize disruptions or delays in treatment. Such integration would be in line with current clinical guidelines and recommendations, supporting a proactive approach to managing complications induced by chemotherapy [7]. Furthermore, gaining a deeper understanding of the most effective protocols and techniques for applying cryotherapy in young patients could enable more tailored and specific treatment approaches [8].

The research findings will serve as a valuable resource for healthcare professionals involved in pediatric oncology, assisting them in making evidence-based decisions about incorporating cryotherapy into clinical practice. Additionally, the study may highlight areas for future research and innovation, potentially leading to the development of novel therapies or enhancements to existing cryotherapy techniques. Furthermore, this study aims to enhance the quality of care and overall health of pediatric cancer patients by exploring the potential benefits of this intervention. This could help mitigate the impact of oral mucositis on their treatment journey. In recent years, numerous studies have explored the effectiveness of oral cryotherapy in preventing oral mucositis. One study evaluated the efficacy of oral cryotherapy in preventing this condition among cancer patients following chemotherapy. The findings indicated that oral cryotherapy significantly reduced the risk of developing oral mucositis, regardless of its severity [9]. Another study, employing a controlled randomized trial (RCT) design, aimed to confirm that oral cryotherapy is an effective solution for managing oral mucositis in patients treated with 5-fluorouracil. The results of this study provide strong evidence supporting the use of oral cryotherapy in the prevention of oral mucositis [10].

A study was conducted to assess the impact of cryotherapy on preventing oral mucositis in pediatric patients undergoing autologous stem cell transplantation with a melphalan-etoposide-carboplatin regimen. This research demonstrates the significant effectiveness of cryotherapy as a preventive measure against melphalan-induced oral mucositis in pediatric patients, with notable clinical significance [11].

A systematic review by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has demonstrated that oral cryotherapy is an effective method for preventing oral mucositis [7]. This recommendation specifically targets two patient groups: (1) those undergoing autologous hematopoietic stem cell transplant with high-dose melphalan conditioning protocols, and (2) patients receiving bolus 5-fluorouracil chemotherapy [5]. A study confirmed that oral cryotherapy effectively prevents oral mucositis [6]. Research indicates that fluorouracil-based chemotherapy for solid tumors can prevent oral mucositis in adults.

Furthermore, it has been effective in preventing severe oral mucositis in adults undergoing high-dose melphalan-based chemotherapy prior to hematopoietic stem cell transplantation [7,12,13].

The cryotherapy protocol employed in this study involves the application of ice packs within the oral cavity, starting five minutes before chemotherapy and continuing for 30 minutes at temperatures ranging from -1°C to 1°C. This approach differs from previous protocols, such as those used by Katrancı et al. [10], which did not specify the timing relative to chemotherapy or the exact temperature range. The idea behind our protocol comes from previous research showing that early application and careful temperature control are crucial for maximizing the effectiveness of cryotherapy in preventing oral mucositis [5,14]. Additionally, the World Health Organization (WHO) oral mucositis scale was employed to provide a standardized assessment of mucositis severity, ensuring consistency and reliability in outcome measurement.

This study sets itself apart from earlier research by specifying when cryotherapy should begin in relation to chemotherapy and by maintaining a precise temperature range. These methodological specifics are grounded in evidence that indicates the importance of early and controlled application for effectively preventing oral mucositis. In contrast, previous studies frequently did not include these detailed specifications, which may have led to inconsistent outcomes. By following a standardized protocol and using the WHO oral mucositis scale, this study seeks to deliver more consistent and reliable results, thus enhancing the effectiveness of cryotherapy practices in pediatric oncology.

The importance of cryotherapy in pediatric oncology is underscored by the considerable discomfort and complications arising from oral mucositis, which can hinder nutritional intake and elevate the risk of infections. Cryotherapy offers a non-invasive and cost-effective method to alleviate these negative outcomes, thus improving the overall treatment experience for children. Safety remains a critical consideration; the protocol implemented in this study ensures a temperature range that is both effective and safe, reducing the possi-

bility of cold-induced injury to the oral tissues.

Further studies will be necessary to confirm these findings across various pediatric populations and different chemotherapy regimens. Further research should investigate the long-term effects of cryotherapy on quality of life and treatment adherence, as well as any potential side effects not identified in the initial studies. Additionally, larger sample sizes and multicenter trials would aid in generalizing the results and refining the protocol for wider applications.

1. Aim

The goal of this study was to determine whether cryotherapy can prevent oral mucositis in pediatric cancer patients by examining its impact on the severity, frequency, and duration of mucositis episodes. Effectiveness was assessed based on the incidence and severity of mucositis, using the WHO Oral Mucositis Scale. Additionally, this study monitored the frequency of mucositis episodes and the duration of each episode from onset to resolution. This comprehensive evaluation will help establish the viability of cryotherapy as a standard preventive treatment in pediatric oncology.

2. Hypothesis

The hypothesis of this study was that cryotherapy significantly reduces the severity, incidence, and duration of oral mucositis episodes in pediatric cancer patients compared to a control group not receiving cryotherapy.

METHODS

Ethical statements: This study was approved by the Institutional Review Board (IRB) of King Hussein Cancer Center (IRB No. 21-KHCC-076). Informed consent was obtained from all participants.

1. Design

The present study was an evidence-based practice that employed an RCT design with two groups: experimental and control. RCTs are pivotal in evidence-based practice as they assist clinicians, policymakers, and healthcare professionals in making informed decisions. They produce high-quality evidence that substantiates the efficacy and safety of interventions, thereby guiding clinical guidelines, treatment recommendations, and healthcare policies [15]. Randomization was rigorously implemented to maintain a robust scientific protocol, utilizing a computer-generated list of random numbers. Allocation was managed by an independent administrator who was not involved in the direct care of the patients, aligning with the research objectives.

To reduce bias, the study employed a single-blind technique in which only the outcome assessors were unaware of the group assignments—either cryotherapy or standard care. This approach ensured unbiased evaluations, despite participants being aware of their treatment type due to the interventions' evident characteristics.

The reporting of this study was based on the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines [16].

2. Sampling and Setting

We approached pediatric cancer patients receiving chemotherapy at a specialized cancer center in Jordan. With a statistical power of 0.8 and assuming a medium effect size and a significance level (α) of 0.05, the total sample size was determined to be 59; these participants were divided into two distinct groups [17]. Throughout the study, there were no dropouts, which is likely attributable to the comprehensive support and follow-up provided.

The study enrolled pediatric patients aged 8 to 18 who had been diagnosed with cancer and were undergoing treatment with either high-dose methotrexate or etoposide chemotherapy regimens. These patients were receiving care at a specialized cancer center in Jordan. However, the study excluded patients with open wounds, oral cavity issues, hypersensitivity to cold, or vascular disease. The safety of cryotherapy in the pediatric population was ensured through meticulous monitoring and carefully designed exclusion criteria to prevent adverse effects.

Exclusion criteria: (1) Patients presenting with open wounds or oral complications were excluded to avoid exacerbating these conditions through cryotherapy. (2) Hypersensitivity to cold was also a crucial exclusion criterion, as it could lead to adverse reactions. (3) Furthermore, individuals with vascular disease were not included in the study, as cryotherapy could adversely impact their blood flow.

3. Data Collection and Procedure

A total of 59 patients were randomly divided into two groups: the experimental group (n=29) and the control group (n=30). The purpose of this randomization was to ensure equivalence between the groups, thereby minimizing bias related to participant characteristics that could affect the study's internal validity. This random assignment aimed to attribute any differences in outcomes specifically to the intervention rather than to extraneous factors. Simple randomization (1:1) was employed, assigning patients with odd numbers to the experimental group. In this group, cryotherapy was administered, while the control group received standard treatment (Figure 1). The intervention period spanned from June 2022 to December 2022.

We ensured the reliability of the oral mucositis assessments by employing healthcare professionals who were both trained and calibrated as assessors, separate from the caregiving team. Standardized assessment procedures were strictly adhered to, and assessors were blinded to the participants' treatment groups to maintain objectivity. Regular inter-rater reliability checks were conducted to ensure consistency across assessments.

In this study, the experimental group underwent a carefully structured cryotherapy protocol. This intervention involved placing ice packs inside the oral cavity, starting 5 minutes before chemotherapy and continuing for a continuous 30-minute period. The ice packs were consistently maintained at temperatures ranging narrowly from -1°C to 1°C. This regimen was followed for each chemotherapy session throughout the duration of the study. To ensure uniform application of cryotherapy across all participants, our nursing staff underwent extensive training on this protocol. We implemented systematic supervision to maintain strict adherence to the specified temperature and timing guidelines. A detailed checklist was used by our medical team to precisely record the start and end times of each session, as well as the temperature of the ice packs. This method was crucial in reducing variability in the intervention, thereby enhancing the credibility and replicability of our findings.

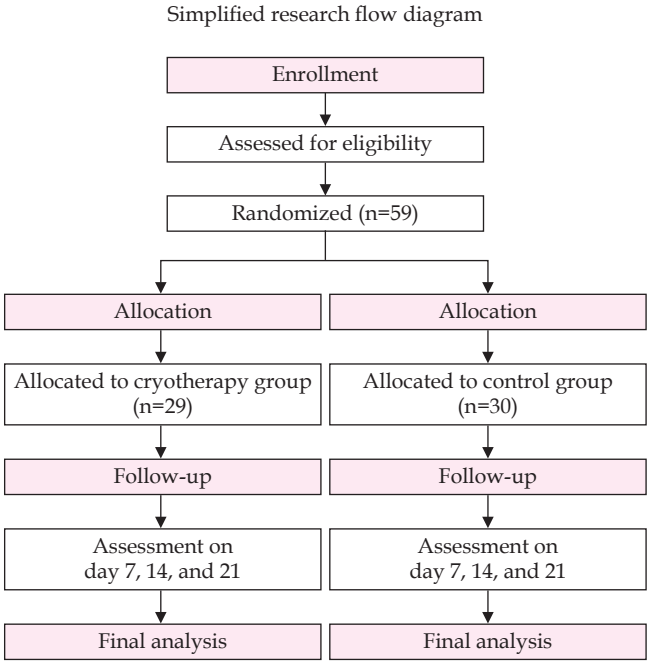

Figure 1. Research flow diagram.

In this study, the control group received the standard care typically administered to pediatric cancer patients undergoing chemotherapy, which did not include cryotherapy. This usual treatment includes several key components: basic oral care, which involves routine oral hygiene using a soft toothbrush and mild toothpaste to minimize mucosal irritation; pain management, where standard analgesics are provided as needed to manage pain associated with oral mucositis; nutritional support, which consists of dietary adjustments and supplementation to ensure adequate nutrition despite oral discomfort; and infection control, involving prophylactic measures such as the use of antimicrobial mouthwashes prescribed by the treating oncologist. These components collectively represent the comprehensive supportive care protocols aimed at managing the side effects of chemotherapy, with a particular focus on the prevention and management of oral mucositis.

4. Outcome Measures

The primary outcome of the study was the prevention of oral mucositis using oral cryotherapy. The WHO oral mucositis scale served as a standardized system to assess the severity of oral mucositis among participants [18]. Trained healthcare professionals evaluated the severity of oral mucositis using the WHO oral mucositis scale at specified intervals. This scale provides a framework for healthcare professionals to evaluate and categorize the extent and severity of oral mucositis in patients. It includes five grades or levels, ranging from 0 to 4, with each grade representing a specific degree of mucositis: grade 0 (no mucositis), grade 1 (mild mucositis), grade 2 (moderate mucositis), grade 3 (severe

mucositis), and grade 4 (life-threatening mucositis). Assessments of oral mucositis were conducted at four different times during the treatment. The initial assessment occurred upon patient admission, establishing a baseline. On day 7, following chemotherapy, patients were evaluated for oral mucositis in the pediatric clinic. Subsequent assessments were carried out on days 14 and 21, corresponding to the second and third cycles of treatment, respectively.

5. Ethical Considerations

Participants were fully informed about the purpose of the study, and it was emphasized that their participation was voluntary and that they could withdraw at any time. The consent process varied depending on the age of the participants. For children aged 8–12, only parental written consent was required, without the need for patient assent. For those aged 12– 15, verbal assent from the patients was obtained in addition to the parental written consent. Participants aged 15–18 provided their own written assent as well as written consent from their parents.

6. Statistical Analysis

Statistical analyses were conducted using SPSS Statistics software version 25.0 (IBM Corp.). The study utilized both descriptive and inferential statistics to analyze the demographic characteristics of the sample. Univariate analysis was used to compare mucositis scores between the experimental and control groups, employing the chi-square test for categorical variables. To account for multiple comparisons resulting from various tests across different days and variables, a Bonferroni correction was applied, adjusting the significance level based on the number of tests conducted.

Control variables in our analysis, including age, sex, type of chemotherapy, and baseline severity of oral mucositis, were matched across the experimental and control groups to minimize confounding factors. These variables were selected due to their known influence on the incidence and severity of oral mucositis among pediatric oncology patients.

RESULTS

1. Overview of Participant Demographics

The study involved 59 participants, who were predominantly males (59.3%), with females making up 40.7%. These participants were diagnosed with various diseases, among which acute lymphoblastic leukemia (ALL) was the most common, representing 61.0% of the cases. Less prevalent conditions, such as Ewing sarcoma, accounted for only 1.7% of the sample. In terms of chemotherapy treatments, high-dose methotrexate was the most commonly used, as it was administered in 66.1% of the cases (Table 1). The participants had an average age of approximately 12.1 years, with ages ranging from 8.0 to 18.0 years. The median age was 12.0 years, with a standard deviation of 3.06 years (Table 2).

2. Sex and Diagnosis-Comparisons

Table 3 illustrates the relationship between different chemotherapy treatment groups, specifically the control and experimental groups, in relation to various factors. Our initial analysis focused on the gender distribution, revealing that the control group, comprising 36.7% females and 63.3% males, did not significantly differ from the experimental group, which consisted of 44.8% females and 55.2% males ($p=0.52$). Additionally, no significant differences were found ($p>0.05$) when examining the incidence of diagnoses such as ALL, acute myeloid leukemia, and B-cell lymphoma, we observed no significant differences between the groups.

3. Reduction in Severity and Incidence Rate of Mucositis

We present data demonstrating a reduction in the severity of mucositis episodes and a decreased incidence rate among patients in the cryotherapy group compared to the control group. These findings are crucial as they confirm the effectiveness of cryotherapy in a clinical setting. The most significant differences between the control and experimental groups were observed during evaluations on days 7, 14, and 21. These evaluations revealed marked differences in treatment responses over time. On day 7, the difference was statistically significant, with a p-value of 0.03. This trend became more pronounced in the day 14 assessment ($p=0.01$), and the day 21 assessment further confirmed the ongoing disparity in response ($p=0.04$). This indicates that the control and experimental groups experienced distinctly different responses to chemotherapy, particularly as the treatment progressed (Table 4).

Table 1. Descriptive Statistics for Categorical Variables (*N*=59)

Variables	Frequency (%)
Sex	
Female	24 (40.7)
Male	35 (59.3)
Diagnosis	
Hematological	
ALL	36 (61.0)
AML	4 (6.8)
Lymphoma	
B-cell lymphoma	10 (16.9)
Solid tumors	
Ewing sarcoma	1 (1.7)
GCT	1 (1.7)
HD	2 (3.4)
Osteosarcoma	5 (8.5)
Hematological total	40 (67.8)
Solid tumors total	9 (15.3)
Type of CTX	
Methotrexate	
COPAD-M3	4 (6.8)
Consolidation III	1 (1.7)
HDMTX	39 (66.1)
Maintenance course #1	2 (3.4)
R-COPAD M3	1 (1.7)
Methotrexate total	47 (79.7)
Etoposide	
ETOPSIDE	4 (6.8)
GCT	1 (1.7)
ICE	1 (1.7)
IE	1 (1.7)
RICE	1 (1.7)
Etoposide total	8 (13.6)
Other	
IGEV	1 (1.7)
Modified UKALL R3	1 (1.7)
Re-induction week III	2 (3.4)
Other total	4 (6.8)
Group	
Control	30 (50.8)
Experimental	29 (49.2)
Assessment on day 7	
No	50 (84.7)
Yes	9 (15.3)
Oral mucositis degree on day 7 (yes)	
First degree	9 (100.0)
Assessment on day 14	
No	45 (76.3)
Yes	14 (23.7)
Oral mucositis degree day 14 (yes)	
First degree	9 (64.3)
Second degree	3 (21.4)
Third degree	2 (14.3)
Assessment on day 21	
No	43 (72.9)
Yes	16 (27.1)
Oral mucositis degree on day 21 (yes)	
First degree	11 (68.8)
Second degree	4 (25.0)
Third degree	1 (6.3)

(Continued to the next page)

Table 1. Continued

"Yes" indicates the presence of oral mucositis on the given day, and "No" indicates the absence of oral mucositis on the given day; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; GCT, germ cell tumor; HD, Hodgkin disease; COPAD, cyclophosphamide, oncovin (vincristine), prednisone, adriamycin (doxorubicin); HDMTX, high-dose methotrexate; ETOPSIDE, etoposide; ICE, ifosfamide, carboplatin, etoposide; IE, Ifosfamide, etoposide; RICE, rituximab, ifosfamide, carboplatin, etoposide; IGEV, ifosfamide, gemcitabine, vinorelbine.

Table 2. Descriptive Statistics for Continuous Variables

Variable	Number	M	Median	Range	Max	Min	SD
Age (year)	59	12.1	12.0	10.0	18.0	8.00	3.06

M, mean; SD, standard deviation.

4. Hypothesis: Cryotherapy Reduces the Severity of Oral Mucositis

The study carefully monitored the progression of oral mucositis. Initially, on day 7, all cases of mucositis were classified as first-degree. By day 14, the severity levels varied, with 64.3% remaining at first-degree, 21.4% escalating to second-degree, and 14.3% advancing to third-degree. By day 21, the majority of cases (68.8%) were still first-degree, while 25.0% had progressed to second-degree, and a smaller fraction (6.3%) had reached third-degree (Table 1). This trend demonstrates a clear increase in the severity of oral mucositis throughout the treatment period. Overall, these findings underscore the significant differences in treatment responses and side effects between the control and experimental groups, highlighting the impact of treatment type on patient outcomes in chemotherapy (Table 4).

DISCUSSION

This study investigated the role of cryotherapy in preventing oral mucositis among pediatric chemotherapy patients, building on existing research while uniquely focusing on a younger demographic. This approach aligns with findings from previous studies [10,14], and the systematic review by

Table 3. Associations Between Variables (Univariate)

Variables	Experiment (n=29)	Control (n=30)	Total (*N*=59)	*p*-value
Sex				0.52
Female	13 (44.8%)	11 (36.7%)	24 (40.7%)	
Male	16 (55.2%)	19 (63.3%)	35 (59.3%)	
Diagnosis				0.78
ALL	19 (65.5%)	17 (56.7%)	36 (61.0%)	
AML	2 (6.9%)	2 (6.7%)	4 (6.8%)	
B-cell lymphoma	3 (10.3%)	7 (23.3%)	10 (16.9%)	
Ewing sarcoma	1 (3.4%)	0 (0.0%)	1 (1.7%)	
GCT	1 (3.4%)	0 (0.0%)	1 (1.7%)	
HD	1 (3.4%)	1 (3.3%)	2 (3.4%)	
Osteosarcoma	2 (6.9%)	3 (10.0%)	5 (8.5%)	
Specific diagnosis				0.42
Hematological	21 (72.4%)	19 (63.3%)	40 (67.8%)	
Lymphoma	3 (10.3%)	7 (23.3%)	10 (16.9%)	
Solid tumors	5 (17.2%)	4 (13.3%)	9 (15.3%)	
Type of CTX				0.63
Etoposide	4 (13.8%)	4 (13.3%)	8 (13.6%)	
Methotrexate	22 (75.9%)	25 (83.3%)	47 (79.7%)	
Other	3 (10.3%)	1 (3.3%)	4 (6.8%)	

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; GCT, germ cell tumor; HD, Hodgkin disease; COPAD, cyclophosphamide, oncovin (vincristine), prednisone, adriamycin (doxorubicin); HDMTX, high-dose methotrexate; ETOPSIDE, etoposide; ICE, ifosfamide, carboplatin, etoposide; IE, ifosfamide, etoposide; RICE, rituximab, ifosfamide, carboplatin, etoposide; IGEV, ifosfamide, gemcitabine, vinorelbine.

Table 4. Univariate Analysis of Oral Mucositis Assessment over Three Time Intervals

Variables	Experiment (n=29)	Control (n=30)	Total (*N*=59)	*p*-value
Assessment on day 7				0.03
No	28 (96.6%)	22 (73.3%)	50 (84.7%)	
Yes	1 (3.4%)	8 (26.7%)	9 (15.3%)	
Assessment on day 14				0.01
No	27 (93.1%)	18 (60.0%)	45 (76.3%)	
Yes	2 (6.9%)	12 (40.0%)	14 (23.7%)	
Assessment on day 21				0.04
No	25 (86.2%)	18 (60.0%)	43 (72.9%)	
Yes	4 (13.8%)	12 (40.0%)	16 (27.1%)	

"Yes" indicates the presence of oral mucositis on the given day, and "no" indicates the absence of oral mucositis on the given day.

the Mucositis Study Group of MASCC/ISOO [7], which have similarly reported positive outcomes with cryotherapy. The observed reduction in mucositis severity is critical as it decreases patient discomfort and potentially improves adherence to cancer therapy. The implications of mitigating oral mucositis are significant, including reduced pain, improved nutritional intake, and a decreased risk of infection [19].

This study closely examined the time-sensitive benefits of cryotherapy for managing oral mucositis in pediatric cancer patients, observing significant results on days 7, 14, and 21 after treatment. The notable early improvement on day 7 highlights the critical importance of initiating cryotherapy promptly. This approach aligns with the findings of Al-Rudayni et al. [14] and is pivotal for mitigating the advancement of mucositis. The early application of cryotherapy has been consistently recommended in various studies, emphasizing its importance in the initial stages of treatment [4].

Over the course of the study, the experimental group showed improvement in mucositis, beginning on day 14 and continuing through day 21. This indicates that cryotherapy was effective throughout the entire study period.

These findings are consistent with the conclusions of the systematic review by the Mucositis Study Group of MASCC/ISOO, demonstrating that the benefits of cryotherapy are not limited to immediate relief but also extend to the ongoing management of oral mucositis. Moreover, the results

observed, especially on day 21, strongly support the incorporation of cryotherapy into standard care protocols for young cancer patients. In line with recent research, these outcomes reinforce the notion that cryotherapy can be effectively used to prevent and treat oral mucositis across various stages of chemotherapy [5,6,11,20].

The consistency of these results with other studies in this field underscores the significant role of cryotherapy in enhancing treatment experiences for pediatric oncology patients. This study advocates for the incorporation of cryotherapy into pediatric cancer care practices, emphasizing its effectiveness in managing one of the most common and challenging side effects of chemotherapy treatments. However, a randomized controlled study by Kamsvåg et al. [21] indicated that oral cryotherapy did not significantly reduce the incidence of severe oral mucositis, oral pain, or the need for opioid medication in young patients undergoing various conditioning treatments for hematopoietic stem cell transplantation.

The current findings align with the broader research landscape, highlighting the effectiveness of cryotherapy in managing oral mucositis, especially within pediatric oncology. This study adds a crucial pediatric-specific viewpoint to the existing body of research, addressing the distinct challenges and needs of children undergoing chemotherapy. The evidence presented supports cryotherapy as an effective, manageable, and child-friendly option for supportive cancer care [22]. By providing data on the effectiveness of cryotherapy in children, this study improves our approach to personalized and age-appropriate treatment strategies in pediatric oncology, emphasizing the significance of proactive and non-pharmacological interventions in the care of young cancer patients.

In summary, this research not only corroborates existing evidence on the benefits of cryotherapy but also enhances our understanding by exploring its application in pediatric cancer care. This significant contribution aids in refining cancer treatment protocols and improving the quality of life for pediatric patients undergoing chemotherapy.

1. Recommendations

1) Clinical application

It is strongly recommended to include cryotherapy in the standard therapeutic protocols for children undergoing chemotherapy. To ensure its effective use, detailed guidelines should be developed. These guidelines must address specific aspects of cryotherapy application, including optimal duration, temperature settings, and timing relative to chemotherapy sessions. Importantly, these protocols should be adapted to meet the unique needs of pediatric patients, considering their distinct physical and psychological responses to treatments.

2) Future research

Extending research into various aspects of cryotherapy is necessary. Future studies should explore its efficacy across different chemotherapy treatments, varying dosages, and diverse patient demographics. Additionally, it is important to focus research on understanding the long-term impacts and quality of life outcomes for patients after cryotherapy to fully appreciate its extended benefits and any potential lasting effects.

2. Limitations

Our study offers valuable insights into the effectiveness of cryotherapy for preventing oral mucositis in pediatric cancer patients, yet it comes with several limitations. The restricted sample size and diversity may hinder the generalizability of our findings to a broader population and other pediatric oncology settings. Additionally, our research did not examine all possible factors influencing the occurrence of mucositis, such as genetics, previous mucositis episodes, or individual oral hygiene practices, which could impact the applicability of our results across different demographic groups. The use of self-reported outcomes for some secondary measures might also introduce response bias. These issues highlight the necessity for future studies to involve larger, more diverse populations and to consider using objective biomarkers of mucositis severity. This approach would not only improve the reliability and relevance of the findings to a wider demographic but also deepen our understanding of the multifactorial nature of mucositis development and prevention.

CONCLUSION

This study highlights the notable effectiveness of cryotherapy in preventing oral mucositis among pediatric cancer patients, demonstrating notable benefits at various stages of their treatment journey. The findings carry important implications for pediatric oncology practice. By incorporating

cryotherapy into treatment protocols, there is a strong potential to enhance the standard of patient care and improve the quality of life for young cancer patients, representing a substantial advancement in their treatment experience.

In conclusion, there is a compelling need to integrate cryotherapy into standard pediatric oncology care practices. Additionally, it is crucial to persist in researching this field to continuously refine and optimize pediatric cancer treatment strategies, ultimately aiming to improve patient outcomes and enhance their quality of life.

ARTICLE INFORMATION

Authors' contribution

Conceptualization: all authors; Data collection and formal analysis: all authors; Writing-original draft: all authors; Writing, reviewing, and editing: all authors; Final approval of the published version: all authors.

Conflict of interest

No existing or potential conflict of interest relevant to this article was reported.

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Data availability

Please contact the corresponding author for data availability.

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REFERENCES

1. Colella G, Boschetti CE, Vitagliano R, Colella C, Jiao L, King-Smith N, et al. Interventions for the prevention of oral mucositis in patients receiving cancer treatment: evidence from randomised controlled trials. Current Oncology. 2023;30(1):967-980. https://doi.org/10.3390/curroncol30010074
2. Bell A, Kasi A. Oral mucositis. In: Aboubakr S, Abu-Ghosh A, Adibi Sedeh P, Aeby TC, Aeddula NR, Agadi S, et al., Editors. StatPearls. 2023.
3. Ribeiro ILA, Melo ACR, Limão NP, Bonan PRF, Lima Neto EA, Valença AMG. Oral mucositis in pediatric oncology patients: a nested case-control to a prospective cohort. Brazilian Dental Journal. 2020;31(1):78-88. https://doi.org/10.1590/0103-6440201802881
4. Allan R, Malone J, Alexander J, Vorajee S, Ihsan M, Gregson W, et al. Cold for centuries: a brief history of cryotherapies to improve health, injury and post-exercise recovery. European Journal of Applied Physiology. 2022;122:1153-1162. https://doi.org/10.1007/s00421-022-04915-5
5. Correa MEP, Cheng KKF, Chiang K, Kandwal A, Loprinzi CL, Mori T, et al. Systematic review of oral cryotherapy for the management of oral mucositis in cancer patients and clinical practice guidelines. Supportive Care in Cancer. 2020;28(5):2449-2456. https://doi.org/10.1007/s00520-019-05217-x
6. Riley P, McCabe MG, Glenny AM. Oral cryotherapy for preventing oral mucositis in patients receiving cancer treatment. JAMA Oncology. 2016;2(10):1365-1366. https://doi.org/10.1001/jamaoncol.2016.2680
7. Elad S, Cheng KKF, Lalla RV, Yarom N, Hong C, Logan RM, Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2020;126(19):4423-4431. https://doi.org/10.1002/cncr.33100
8. Lee CC, Kuo SF, Chang WP, Guo SL, Huang TW. Effectiveness of cryotherapy on cancer therapy-induced oral mucositis: an umbrella review. Cancer Nursing. 2023;46(5):E288-E296. https://doi.org/

10.1097/ncc.0000000000001128
9. Al-Rudayni AHM, Gopinath D, Maharajan MK, Veettil SK, Menon RK. Efficacy of photobiomodulation in the treatment of cancer chemotherapy-induced oral mucositis: a meta-analysis with trial sequential analysis. International Journal of Environmental Research and Public Health. 2021;18(14):7418. https://doi.org/10.3390/ijerph18147418
10. Katrancı N, Ovayolu N, Ovayolu O, Sevinc A. Evaluation of the effect of cryotherapy in preventing oral mucositis associated with chemotherapy - a randomized controlled trial. European Journal of Oncology Nursing. 2012;16(4):339-344. https://doi.org/10.1016/j.ejon.2011.07.008
11. Kawaguchi K, Umeda K, Takachi T, Ogura T, Horikoshi Y, Saida S, et al. Effects of cryotherapy on high-dose melphalan-induced oral mucositis in pediatric patients undergoing autologous stem cell transplantation. Pediatric Blood & Cancer. 2020;67(9):e28495. https://doi.org/10.1002/pbc.28495
12. Griffiths C, Kwon N, Beaumont JL, Paice JA. Cold therapy to prevent paclitaxel-induced peripheral neuropathy. Supportive Care in Cancer. 2018;26(10):3461-3469. https://doi.org/10.1007/s00520-018-4199-9
13. Lilleby K, Garcia P, Gooley T, McDonnnell P, Taber R, Holmberg L, et al. A prospective, randomized study of cryotherapy during administration of high-dose melphalan to decrease the severity and duration of oral mucositis in patients with multiple myeloma undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplantation. 2006;37(11):1031-1035. https://doi.org/10.1038/sj.bmt.1705384
14. Al-Rudayni AHM, Gopinath D, Maharajan MK, Veettil SK, Menon RK. Efficacy of oral cryotherapy in the prevention of oral mucositis associated with cancer chemotherapy: systematic review with meta-analysis and trial sequential analysis. Current Oncology. 2021;28(4):2852-2867. https://doi.org/10.3390/curroncol28040250
15. Ahuja AS. Should RCT's be used as the gold standard for evidence based medicine? Integrative Medicine Research. 2019;8(1):31-32. https://doi.org/10.1016/j.imr.2019.01.001
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Journal of Clinical Epidemiology. 2008;61(4):344-349. https://doi.org/10.1016/j.jclinepi.2007.11.008
17. Cohen J. A power primer. Psychological Bulletin. 1992;112(1):155-159. https://doi.org/10.1037//0033-2909.112.1.155
18. Stiff PJ, Emmanouilides C, Bensinger WI, Gentile T, Blazar B, Shea TC, et al. World Health Organization Oral Mucositis Scale (WHO Oral Mucositis Scale) [Internet]. 2006 [cited 2024 July 17]. Available from: https://eprovide.mapi-trust.org/instruments/world-health-organization-oral-mucositis-scale
19. Patel P, Robinson PD, Baggott C, Gibson P, Ljungman G, Massey N, et al. Clinical practice guideline for the prevention of oral and oropharyngeal mucositis in pediatric cancer and hematopoietic stem cell transplant patients: 2021 update. European Journal of Cancer. 2021;154:92-101. https://doi.org/10.1016/j.ejca.2021.05.013
20. Alsulami FJ, Shaheed SU. Oral cryotherapy for management of chemotherapy-induced oral mucositis in haematopoietic cell transplantation: a systematic review. BMC Cancer. 2022;22(1):442. https://doi.org/10.1186/s12885-022-09539-8
21. Kamsvåg T, Svanberg A, Legert KG, Arvidson J, von Essen L, Mellgren K, et al. Prevention of oral mucositis with cryotherapy in children undergoing hematopoietic stem cell transplantations-a feasibility study and randomized controlled trial. Supportive Care in Cancer. 2020;28(10):4869-4879. https://doi.org/10.1007/s00520-019-05258-2
22. Garcia C, Karri J, Zacharias NA, Abd-Elsayed A. Use of cryotherapy for managing chronic pain: an evidence-based narrative. Pain and Therapy. 2021;10(1):81-100. https://doi.org/10.1007/s40122-020-00225-w