Oral Cryotherapy for Oral Mucositis in Patients Receiving Busulfan: A Retrospective/Prospective Descriptive Study

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OBJECTIVES: To determine whether oral cryotherapy (OC) mitigates oral mucositis (OM) resulting from busulfan chemotherapy.

SAMPLE & SETTING: Electronic health records of patients undergoing busulfan conditioning for blood and marrow transplantation were reviewed for this descriptive study. The post-OC group received OC with busulfan, but the pre-OC group did not.

METHODS & VARIABLES: Demographic and disease characteristics for both groups were summarized using descriptive statistics. Wilcoxon rank-sum test was performed for continuous and ordinal measures, and chi-square tests were performed for categorical outcomes between the two groups.

RESULTS: This study found a decrease in the severity of OM as assessed by the World Health Organization OM scale. This study also found a reduction of total parenteral nutrition and opioid pain medication use, as well as a decrease in length of stay and airway protection–related intensive care unit transfers. An increase in day 11 methotrexate administration for graft-versus-host disease prophylaxis was observed in the post-OC group.

IMPLICATIONS FOR NURSING: OC is a safe and easily implemented intervention that can decrease OM in patients receiving busulfan chemotherapy.

KEYWORDS chemotherapy; oral mucositis; busulfan; oral cryotherapy; cryotherapy; conditioning

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Various myeloablative chemotherapy regimens are used as conditioning prior to blood and marrow transplantation (BMT). Conditioning regimens are based on patient-specific factors and frequently require combination chemotherapy. Two antineoplastic agents used in the BMT population, melphalan and busulfan, are associated with high rates of oral mucositis (OM) (Niscola et al., 2007). Busulfan has also been associated with gastrointestinal toxicity, hepatotoxicity, seizures, and acute graft-versus-host disease (GVHD) (Weil et al., 2017). OM is characterized by the inflammation of the oral and oropharyngeal cavity and most commonly occurs five to seven days after high-dose chemotherapy, persisting for at least six days and resolving with count recovery after BMT (Salvador et al., 2012). The clinical consequences of OM include dehydration, malnutrition, infection, and possibly reduced long-term survival in patients with hematologic neoplasia (Batlle et al., 2014; Riley et al., 2015).

Patients with severe OM are often at risk for more complex symptoms, potentially requiring longer hospitalization and increasing the healthcare costs of therapeutic care compared to patients with limited or no OM (Salvador et al., 2012). Reducing OM can have a positive effect on organizational and unit-based goals. Organizational goals that are affected by OM include length of stay (LOS), treatment costs, and patient satisfaction (Niscola et al., 2007). Unit-based goals that are affected include quality of life, food intake, pain, dysphagia, infections, use of total parenteral nutrition (TPN), and time in the intensive care unit (ICU) (Niscola et al., 2007).

OM presents potential risks for all patients, but there is also an increased risk of GVHD for patients

FIGURE 1. World Health Organization Oral Mucositis Scale

- Grade 0 (none): None
- Grade 1 (mild): Oral soreness, erythema
- Grade 2 (moderate): Oral erythema, ulcers, solid diet tolerated
- Grade 3 (severe): Oral ulcers, liquid diet only
- Grade 4 (life-threatening): Oral alimentation impossible

Note. Based on information from World Health Organization, 1979.

undergoing BMT. Low-dose methotrexate plays an important role in GVHD prophylaxis, but its administration can also cause continued leukocyte count suppression, potentially increasing OM duration and severity (Cutler et al., 2005). If day 11 methotrexate is held because of severe OM, there can be a direct influence on patient outcomes. The benefit of administering all four doses of methotrexate as GVHD prophylaxis must be weighed against the potential for continued count suppression in patients experiencing severe OM.

Although many different agents have been studied for the prevention of OM, oral cryotherapy (OC) is a safe, inexpensive, and easily implemented nursing intervention that can potentially reduce OM. OC causes vasoconstriction and decreased blood flow to the oral cavity, thereby reducing the exposure of the buccal mucosa to cytotoxic drugs (Batlle et al., 2014; Gori et al., 2007; Svanberg et al., 2010). There is a significant amount of literature on the use of OC to decrease the risk and severity of OM with melphalan, but there is limited literature on the efficacy of OC in conjunction with busulfan conditioning (Correa et al., 2019; Elad et al., 2020; Niscola et al., 2007; Stone et al., 2005). The primary aim of this study is to determine whether OC mitigates OM associated with busulfan. The secondary aims of this study are to observe any effect administration of OC with busulfan may have on LOS, ICU transfer for airway protection, TPN, opioid use for OM, and day 11 methotrexate use.

This study and its results can be supported by Watson's Caring Model. This theoretical framework, created by Jean Watson, is grounded in health promotion and a unique way of coping with the environment. Watson emphasized the value of human beings and that they should be cared for, respected, nurtured, and assisted (Petiprin, 2020). By decreasing OM severity, TPN, opioid administration, LOS, and ICU transfers, as well as by increasing day 11 methotrexate use, better patient health and outcomes can be achieved. OC during busulfan chemotherapy helps promote better health and improved outcomes for patients by decreasing chemotherapy side effects and providing increased comfort during their BMT.

Methods

This study used a retrospective/prospective review of the electronic health record (EHR) for patients receiving busulfan chemotherapy. Records of patients conditioned for BMT using fludarabine along with either two or four days of busulfan between January 2015 and December 2018 were reviewed. Records from January 2015 to December 2016 are the pre-OC group, and records from January 2017 to December 2018 are the post-OC group. Patients receiving matched related donor or matched unrelated donor transplantations were included. Cell sources included peripheral blood stem cells and marrow. Patients were excluded if they received any other conditioning regimen for their BMT or if their cell source was anything other than peripheral blood stem cells or marrow. Patients who died prior to engraftment were also excluded.

Sample and Setting

This study was conducted on a 32-bed hematology, oncology, and BMT unit at a 500-bed American Nurses Credentialing Center Magnet-designated academic medical center. The transplantation unit is accredited by the Foundation for the Accreditation of Cellular Therapy. The unit averages 107 inpatient BMTs per year. This study used a nonrandomized convenience sample of patients receiving busulfan chemotherapy as part of their transplantation conditioning regimen. Because OC with busulfan was implemented as a standard of care prior to this study, the sample was not randomized. The sample size was determined by past and current admission numbers for patients undergoing BMT. The study was approved by the Medical College of Wisconsin Institutional Review Board.

Intervention

OC in conjunction with busulfan infusions was initiated as a standard of care in January 2017. An OC policy was developed and implemented in collaboration with nursing and pharmacy. The length of time that patients are asked to perform OC is based on busulfan pharmacokinetics, peak drug concentrations, and literature review of how long patients can reasonably undergo OC. Studies have shown that patients can tolerate OC

for up to 120 minutes (Aisa et al., 2005; Mori et al., 2006). In a study by Lilleby et al. (2006), participants were asked to perform OC for a total of seven hours (30 minutes prior to melphalan infusion, during infusion, and for 6 hours after). In the study, only 14 of the 21 participants were able to tolerate OC for longer than five hours after infusion. Some participants complained about the coldness of the ice chips, so they stopped using them. Because no studies discussed the timing of OC with busulfan, unit pharmacists developed the timing of OC in reference to established pharmacokinetics. Considering the feasible duration for OC to be 120 minutes, unit pharmacists used expected busulfan clearance rates to determine the optimal timing for OC to coincide with as much busulfan peak concentration and exposure as possible. The optimal start time was determined to be 60 minutes after the start of a two-hour infusion and 90 minutes after the start of a three-hour infusion. Once the policy was developed, staff were educated about the policy change during staff meetings and in the unit newsletter. All patients undergoing transplantation and cellular therapy have a personalized road map that nurses follow during the transplantation course. This road map contains a daily calendar of drugs to be administered to the patient, along with nursing considerations for each drug. For patients receiving busulfan, OC is listed on the road maps to remind nurses to administer OC during busulfan infusions.

Before the administration of busulfan, patients are educated on the need to keep their mouth, throat, and lips cold during the infusion. They are given the options of ice water, ice chips, popsicles, and ice cream. OC with busulfan begins either 60 minutes (for a two-hour infusion) or 90 minutes (for a three-hour infusion) after the infusion is initiated and lasts until 30 minutes to one hour after the infusion is complete, for a total of 120 minutes. Patients are instructed to move ice chips or popsicles around in their mouths, including their buccal mucosa. They are also encouraged to take sips of ice water every few minutes to keep the palate soft and throat cold. Patients are encouraged to use popsicles to keep their lips cold and decrease the chance of sores on the lips.

As a standard of care, all patients undergoing BMT, regardless of conditioning regimen, are instructed to brush their teeth with a soft bristled toothbrush four times a day (after each meal and at bedtime) and to rinse their mouths with normal saline after brushing. This instruction is given by transplantation coordinators before patient admission, is reinforced on admission, and is continually reinforced throughout their stay. No other OM prevention interventions are used for patients receiving two or four days of busulfan conditioning.

Data Collection

Research team members collected data through a review of the EHR for patients receiving busulfan. Data collected included gender, age, diagnosis, conditioning regimen, related or unrelated donor, and stem cell source. OM was assessed using the World Health Organization (WHO) oral mucositis scale. The WHO scale is a system for grading mucositis and uses parameters including clinical appearance and functional status. This scale evaluates various components of OM, including symptoms, anatomic changes,

TABLE 1. Sample Characteristics

Characteristic	$\bar{X}$	SD	Median	Range
Age (years)				
Total (N = 177)	57.8	11.3	60	22–76
Pre-OC (N = 89)	58	10.8	62	26–73
Post-OC (N = 88)	57.6	11.8	60	22–76
			Pre-OC (N = 89)	**Post-OC (N = 88)**
Characteristic			**n**	**n**
Gender				
Male			51	60
Female			38	28
Diagnosis, grouped				
Acute leukemia			47	43
MDS/MF			23	30
Non-Hodgkin lymphoma			8	6
Chronic leukemia			8	5
Hodgkin lymphoma			1	4
Other			2	–
Conditioning regimen				
Flu/Bu2			45	45
Flu/Bu4			42	42
Flu/Bu3			2	1
Related/unrelated				
MUD			51	52
MRD			38	36

Flu/Bu—fludarabine/busulfan; MDS/MF—myelodysplastic syndromes/myelofibrosis; MRD—matched related donor; MUD—matched unrelated donor; OC—oral cryotherapy

TABLE 2. Patient Outcomes by Group

Variable	Pre-OC (N = 89) n	Post-OC (N = 88) n	p
Maximum WHO score[a]			< 0.001**
0	8	16	–
1	17	22	–
2	10	18	–
3	37	27	–
4	17	5	–
Day 11 methotrexate held[b]			0.03*
No	74	78	–
Yes	13	4	–
ICU transfer for airway protection			0.059
No	84	88	–
Yes	5	–	–
Pain medications for mucositis			< 0.001**
Yes	68	46	–
No	21	42	–
TPN use			0.013*
No	62	75	–
Yes	27	13	–

* p ≤ 0.05; ** p ≤ 0.001
ICU—intensive care unit; OC—oral cryotherapy; TPN—total parenteral nutrition; WHO—World Health Organization
[a] The WHO score was used to rate oral mucositis from grade 0 (none) to grade 4 (life-threatening). The mean maximum WHO scores were 2.4 (SD = 1.3) for the pre-OC group and 1.8 (SD = 1.2) for the post-OC group.
[b] Patients who did not receive methotrexate for graft-versus-host disease prophylaxis were excluded from the day 11 methotrexate count. Two patients in the pre-OC group were excluded; one because of an adverse reaction and the other because they received a syngeneic transplantation. Six patients in the post-OC group had post-transplantation Cytoxan for graft-versus-host disease prophylaxis instead of methotrexate.

and functional status (see Figure 1). The WHO OM scale is the standard for measuring OM. In a study comparing the reliability and validity of instruments for the clinical assessment of OM, the WHO scale for OM was found to be a stronger clinical measure of OM than other prominent OM scales, including those by the Radiation Therapy Oncology Group and Western Consortium for Cancer Nursing Research (Stiff et al., 2006). The nurses on the unit use the WHO scale as part of their daily assessments.

The maximum WHO score of each patient was recorded, and LOS was recorded directly from the patient care snapshot in the EHR. TPN administration was obtained from review of the Medication Administration Record (MAR) in the EHR. This study only considered TPN if it was provided because of OM. The BMT team follows specific TPN initiation guidelines and documents the indication for use in the patient progress notes. Along with the MAR, provider progress notes were reviewed to establish indication for TPN. ICU transfer was found in the admission/event information report in the EHR. Indication for transfer was found in the BMT team progress note. Pain medication indication was determined from the vital sign flow sheet in the EHR. This study only considered opioid pain medications if administered for OM. The research team recorded duration of pain medication use, number of oral administration (PO) days, number of IV administration days, and number of patient-controlled analgesia (PCA) days. Because of inability to perform a pain assessment while the patient is intubated, pain medications administered after transfer of patients to the ICU and for the duration of their stay were excluded from data collection. Day 11 methotrexate administration was obtained by review of the MAR in the EHR. Indication for methotrexate being held was found in the BMT team progress note.

Results

Demographic and disease characteristics for both cohorts were summarized using descriptive statistics. Variables for analysis were selected based on their association with sequelae of mucositis and on implications to the patient, nursing, or health system. Wilcoxon rank-sum test was performed for continuous and ordinal measures, and chi-square tests were performed for categorical outcomes between the two cohorts.

A total of 177 patients were eligible for this study. The pre-OC group consisted of 89 patients, and the post-OC group of 88. The demographic, conditioning regimen, and related versus unrelated donor data were similar in both groups (see Table 1).

Of the 88 patients in the post-OC group, 27 developed grade 3 OM, and five developed grade 4 OM; of the 89 patients in the pre-OC group, 37 developed grade 3 OM, and 17 developed grade 4 OM ($p < 0.001$). There was also variation between groups in rate of grades 0, 1, and 2 OM. In the post-OC group, 16 patients developed grade 0 OM, 22 patients developed grade 1 OM, and 18 patients developed grade

2 OM. In contrast, in the pre-OC group, 8 patients developed grade 0 OM, 17 patients developed grade 1 OM, and 10 patients developed grade 2 OM.

In the post-OC group, the mean WHO score decreased from 2.4 to 1.8 ($p < 0.001$). Twenty-seven patients required TPN in the pre-OC group, whereas 13 required TPN in the post-OC group ($p = 0.013$). There was no significant difference between the number of days patients received TPN. No patients in the post-OC group required transfer to ICU for airway protection, but five patients in the pre-OC group required transfer to the ICU for airway protection ($p = 0.059$). Day 11 methotrexate was held because of OM severity in 13 patients in the pre-OC group and was held for 5 patients in the post-OC group ($p = 0.03$) (see Table 2). Mean LOS decreased in the post-OC group from 29.2 days (SD = 10.5) to 24.2 days (SD = 4.1) ($p < 0.001$). The median LOS for the post-OC group was 24 days and for the pre-OC group was 29.2 days (range = 17–91) (see Table 3).

Pain medication use was compared between the two groups. The study examined route of administration (PO, IV, and PCA) and duration of use for each route. Overall, fewer patients required any pain medication regardless of route in the post-OC group ($n = 46$) versus pre-OC ($n = 68$) ($p < 0.001$). Mean duration of pain medication use was less in the post-OC group than in the pre-OC group. Duration in the pre-OC group was 7.3 (SD = 7.2), compared to 4.5 (SD = 4.3) in the post-OC group. Sixty-six patients in the pre-OC group and 44 patients in the post-OC group used the PO route.

The mean PO days varied from 4.2 (SD = 2.7) in the pre-OC group to 5 (SD = 3.4) in the post-OC group. Thirty-four patients in the pre-OC group and 24 patients in the post-OC group used the IV route. The mean IV days increased from 3.6 (SD = 3.7) in the pre-OC group to 4.6 (SD = 3.1) in the post-OC group. In the pre-OC group, 34 patients used a PCA route; in the post-OC group, 19 patients used a PCA route. The mean PCA days decreased from 9.2 (SD = 4.2) in the pre-OC group to 6 (SD = 3.7) in the post-OC group.

The overall results demonstrate the effectiveness of OC for patients receiving busulfan, as established by statistically significant reduced maximum WHO score, reduced LOS, reduced TPN and opioid use for OM, and increased day 11 methotrexate administration (see Table 4).

Discussion

One of the major side effects of busulfan is OM. Moderate to severe OM causes pain and difficulty eating, interfering with nutrition and quality of life in patients undergoing BMT. Therefore, effective prophylaxis of OM is required for achieving a more positive BMT outcome (Aisa et al., 2005). Many studies have demonstrated the benefits of OC during chemotherapy treatment with regard to OM. A systematic review of mucositis management published by Lalla et al. (2014) showed strong evidence to support

TABLE 3. Comparison of Durations of Interventions for Pre- and Post-OC Groups (Days)

Intervention	N	$\bar{X}$	SD	Median	Range	p
Duration of pain medication use						0.002*
Total	177	5.9	6.5	5	0–44	–
Pre-OC	89	7.3	7.2	7	0–44	–
Post-OC	88	4.5	5.3	1.5	0–25	–
Duration of TPN use						0.29
Total	177	12.6	9	10	4–52	
Pre-OC	89	13.7	10.3	10	4–52	
Post-OC	88	10.4	5.4	10	5–27	
Length of stay						< 0.001**
Total	177	26.7	8.4	25	17–91	–
Pre-OC	89	29.2	10.5	26	19–91	–
Post-OC	88	24.2	4.1	24	17–41	–

* $p \leq 0.01$; ** $p \leq 0.001$
OC—oral cryotherapy; TPN—total parenteral nutrition

TABLE 4. Pain Medication Use by Route

	Pre-OC (N = 89)	Post-OC (N = 88)	
Variable	**n**	**n**	**p**
Any PO medications			< 0.001***
Yes	66	44	
No	23	44	
Any IV medications			0.121
No	55	64	
Yes	34	24	
Any PCA			0.016*
No	55	69	
Yes	34	19	
Duration of Intervention	**Median**	**Range**	**p**
PO days, if any PO			0.295
Total (N = 177)	4	1–17	–
Pre-OC (N = 89)	4	1–11	–
Post-OC (N = 88)	4	1–17	–
IV days, if any IV			0.154
Total (N = 177)	3	1–22	–
Pre-OC (N = 89)	3	1–22	–
Post-OC (N = 88)	3.5	1–10	–
PCA days, if any PCA			0.002**
Total (N = 177)	7	1–24	–
Pre-OC (N = 89)	8	4–24	–
Post-OC (N = 88)	5	1–17	–

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001
OC—oral cryotherapy; PCA—patient-controlled analgesia; PO—oral administration

administration of OC during 5-fluorouracil chemotherapy. Another systematic review by Peterson et al. (2012) supports the use of OC for both 5-fluorouracil and melphalan chemotherapy.

Cryotherapy is an intervention recommended for the prevention of OM based on the Oncology Nursing Society (n.d.) Putting Evidence Into Practice resources, which discuss the benefit of vasoconstriction in reducing exposure to mucotoxic drugs.

To date, extensive literature supports the use of OC for reducing OM severity scores, but limited research investigates other benefits of OC. Salvador et al. (2012) determined that cryotherapy for melphalan chemotherapy resulted in a reduced OM severity score, less overall pain scores, and less use of IV morphine or equivalent. Lilleby et al. (2006) found that administration of OC with melphalan infusions resulted in less opioid use, less TPN administration, lower average pain scores, and less difficulty with eating, drinking, talking, and sleeping.

This descriptive study primarily examined the effect of OC on the severity of OM resulting from busulfan administration. As a secondary objective, this study reviewed the effect that OC in conjunction with busulfan has on LOS, ICU transfer for airway protection, TPN and opioid use for OM, and day 11 methotrexate use. This study found a decrease in the severity of OM as assessed in accordance with the WHO scale (grades 3–4 60.7% pre-OC versus 36.4% post-OC). This study also showed a reduction in TPN use (30.3% pre-OC versus 14.8% post-OC). There was no difference in the duration of TPN use between the two groups. If TPN was needed, it was needed for the same amount of time for both groups. Although not statistically significant, there were five ICU transfers for airway protection in the pre-OC group and zero

ICU transfers for airway protection in the post-OC group. Day 11 methotrexate was held 14.9% of the time pre-OC and only 4.9% of the time post-OC. This finding is important when considering potential long-term complications for the patient undergoing BMT. LOS is an important metric for patients and hospitals. This study showed a five-day decrease in mean LOS between pre- and post-OC groups. Decreasing the LOS has an impact on patient quality of life while also playing a role in hospital quality metrics. Pain medication use (PO, IV, and PCA) decreased from 76.4% pre-OC to 52.3% post-OC. The increase in duration of PO and IV pain management in the post-OC group may be attributed to the decrease in PCA pain management.

Limitations

Limitations of this study include that it is a nonrandomized treatment study, making it difficult to correlate administration of OC to decreased incidence or severity of OM in patients. In addition, the uncertainty of patient adherence to OC could limit findings. It is not possible to assess adherence to OC and length of time of OC. Although nursing staff educate each patient on the importance, proper technique, and target duration of OC, not all patients perform OC the way in which they are taught. The EHR does not include an area to document whether OC was performed correctly, and nursing staff do not consistently include adherence to OC in their progress notes. Another potential limitation is that in the pre-OC group, busulfan infusions were given four times a day, but in the post-OC group, busulfan infusions were given once a day. Both groups were dosed based on the same guidelines, but it is not possible to determine whether administering a daily dose in four infusions throughout the day versus one infusion per day has any effect on development of OM. At the authors' center, OC has been used with melphalan since 2007. Before the institution of OC as a standard of care during busulfan administration, anecdotal reports indicate that some nurses had already been giving patients OC with busulfan. This may, in turn, confound the findings in this study. Some variables that could also have an effect on the data include not controlling for oral hygiene, dentures and dental appliance use, and history of oral lesions (Barasch & Peterson, 2003).

Implications for Nursing

This study provides preliminary data on the effects of administering OC in conjunction with busulfan chemotherapy. Using OC with busulfan can translate to cost savings for the patient and organization because of reduced use of TPN and shorter LOS. Increasing day 11 methotrexate administration may also lead to cost savings by reducing GVHD and the costs associated with its treatment. Decreasing the use of pain medication in all forms (PO, IV, PCA) leads to less monitoring and saves nursing time. Even more importantly, patients may experience less pain and greater comfort during and after treatment. Overall, OC may help nurses support patients by reducing discomfort and pain and increasing quality of life during the hospital stay.

KNOWLEDGE TRANSLATION

- Oral cryotherapy (OC) can decrease oral mucositis in patients receiving busulfan chemotherapy.
- OC is a safe and easily implemented nursing intervention.
- With OC use, patients may experience less discomfort or pain and have increased comfort and quality of life during their hospital stay.

Conclusion

OC is a low-cost, nurse-driven, easily implemented intervention. OC shows benefit in decreasing OM severity, LOS, ICU transfers for airway protection, TPN use, and opioid use for OM in patients receiving busulfan as part of their conditioning. These decreases translate into cost savings for patients and organizations. Ultimately, OC can lead to better outcomes for patients, decreasing pain and increasing comfort during a demanding and difficult treatment period.

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