Journal of Oncology Research and Therapy
Dembla V, et al. Oncol Res Ther 10: 10273.
www.doi.org/10.29011/2574-710X.10273
www.gavinpublishers.com

OPEN ACCESS

GAVIN PUBLISHERS

Research Article

Effectiveness of A Reusable, Self-Contained Cryotherapy Delivery Device on Mitigating the Use and Intensity of Analgesics in Patients Being Treated with Cycled Cancer Chemotherapy: Results of A Multi-Institutional, Randomized, Controlled Trial

Vikas Dembla[1], Katherine Corbett[2], Rosemarie Velasquez[2], Kristen Wilson[1], Indrea Jackson[1], Richard Zuniga[2], Frank Jacobucci[3], Stephen Sonis[4,5,*]

[1]Gibbs Cancer Center, Spartanburg, SC, USA.

[2]New York Cancer and Blood Specialists, Port Jefferson Station, NY, USA.

[3]ChemoMouthpiece, LLC, Closter, NJ, USA.

[4]Dana-Farber Cancer Institute, Boston, MA, USA.

[5]Primary Endpoint Solutions, Waltham, MA, USA.

***Corresponding author:** Stephen Sonis, Primary Endpoint Solutions, Waltham, MA, USA.

Citation: Dembla V, Corbett K, Velasquez R, Wilson K, Jackson I, et al. (2025) Effectiveness of A Reusable, Self-Contained Cryotherapy Delivery Device on Mitigating the Use and Intensity of Analgesics in Patients Being Treated with Cycled Cancer Chemotherapy: Results of A Multi-Institutional, Randomized, Controlled Trial. J Oncol Res Ther 10: 10273. DOI: 10.29011/2574-710X.10273.

Received Date: 04 April, 2025; **Accepted:** 11 April, 2025; **Published Date:** 14 April, 2025.

Abstract

Oral mucositis (OM) is a painful complication in patients undergoing cytotoxic chemotherapy (CT) which impacts patients' quality of life and threatens treatment tolerance. Cryotherapy using ice chips has been effective in allaying OM symptoms in short half-life agents but has posed challenges associated with patient compliance and logistics. This study evaluated the efficacy of a reusable, self-administered cryotherapy device in mitigating analgesic use among patients receiving stomatotoxic chemotherapy (SCT). This was a multi-institutional trial in which patients planned to receive at least two cycles of SCT were randomized into two arms (2:1): best supportive care (BSC) with the cryotherapy device or BSC alone. Device use was initiated during chemotherapy infusion and continued at home for five days post-infusion. Daily diaries recorded all forms of analgesic use that were attributable to oral pain. Statistical analysis compared analgesic use between the two groups across two chemotherapy cycles.

Device use significantly reduced the necessity for all forms of analgesic use, including opioids, non-opioids and rescue medications. Patients in the device arm reported fewer days of analgesic use compared to controls, with the reduction being more pronounced in the second cycle.

Key words: Oral Mucositis; Cryotherapy; Analgesics; Opioid; Chemotherapy.

Introduction

Oral mucositis (OM) is a frequent, significant and debilitating complication of cytotoxic chemotherapy [1]. Characterized by painful inflammation and ulceration, OM presents a considerable challenge not only to patient comfort and quality of life, but also to the continuity and efficacy of treatment. The level of OM-associated oral pain often results in difficulty eating, the need for supplemental nutrition, and increased risk of infection [2]. Perhaps most critically, continuing OM during cycled therapy is often cited as a reason for patients discontinuing treatment or a reduction in treatment intensity [3].

The incidence and severity of OM are influenced by a range of factors including the chemotherapeutic agents used, treatment schedules and intensity, and patient-related variables including age, genetics, and comorbidities. While some chemotherapy regimens are associated with a higher risk of OM, standard treatment protocols have also been shown to cause significant mucosal injury in a large proportion of patients. Reports suggest that approximately 40% of individuals receiving conventional chemotherapy experience OM, though this is likely to be an underestimation [4].

Despite its prevalence, OM treatment options are frustratingly inadequate. Supportive agents such as gels and rinses have been deemed ineffective against symptoms [5-8]. Cryotherapy, however, has been well established as a pain mitigator and proven to reduce analgesic use [9-12]. Recent studies have associated cryotherapy with fewer reported incidences of OM and reduced analgesic use in fluorouracil-based regimens as well as high-dose melphalan chemotherapy. It is theorized that cold-induced vasoconstriction reduces the exposure of oral tissues to cytotoxic drugs, thereby minimizing damage to the mucosal cells.

However, the practical application of cryotherapy can be challenging. Patients rely on ice chips which melt, require replenishment, and do not uniformly cool the oral cavity. They also contribute to patient discomfort through drooling, teeth pain, headache, and nausea [13]. Additionally, it has been suggested that water quality, especially in the context of bacterial contamination might impose a risk of infection when ice chips are used in myelosuppressed cancer patients [14]. An alternative to ice chips has been the introduction of cryotherapy devices which provide intraoral cooling. Generally intended for in-hospital or in-clinic use, this type of equipment consists of a unit that cools water which then circulates to an intraoral appliance to cool the mucosa. This configuration confines use to institutional settings. Alternatively, the Chemo Mouthpiece device was designed as a more efficient and comfortable solution to deliver cryotherapy in the clinic and for home use. (Figure 1). The latter is particularly desirable as it enables continuing cold treatment for patients receiving treatment regimens which include agents with long or short half-lives.

In a recent Phase 3b study in which the efficacy of a self-contained cryotherapy device was assessed, patients randomized to the cryotherapy device cohort experienced less pain with respect to incidence and duration than did patients using best supportive care [15]. To better understand the impact of local device delivered cryotherapy on oral mucosal pain management, in this study we compared differences in non-opioid and opioid analgesic use and rescue medications the first 14 days of two consecutive chemotherapy cycles between patients who used the device compared to those who did not.

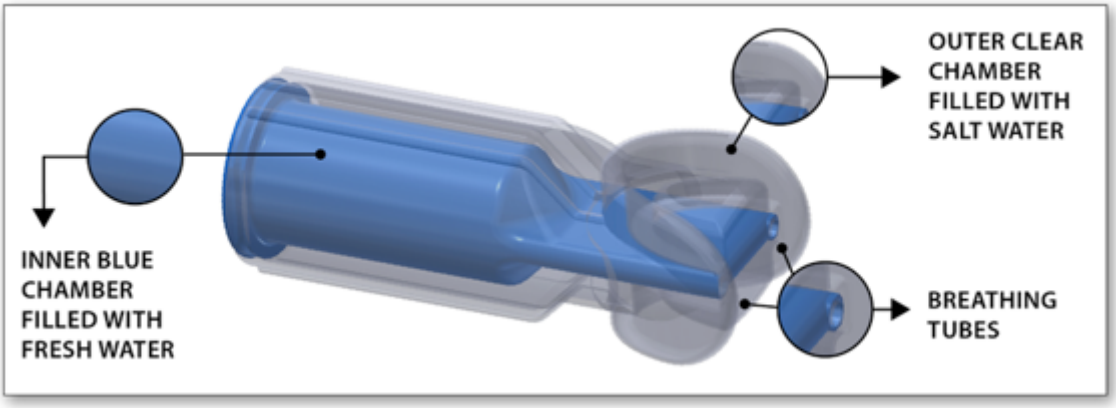

Figure 1: Structure and composition of Chemo Mouthpiece cryotherapy device.

Methods

Overall Study Design

We previously reported the results of a randomized-prospective, multi-center study which evaluated the efficacy of a self-administered oral cryotherapy device as an adjunct to best supportive oral care in reducing symptoms and analgesic use of chemotherapy-induced oral mucositis in patients receiving standard stomatotoxic chemotherapy [15]. This manuscript provides a granular comparison of analgesic use between the control and test cohorts in that trial.

All subjects were consented prior to study start. Study participants were adults (ages 18-80 years) who were planned to receive at least two cycles of an infused stomatotoxic chemotherapy regimen at 16 study sites in the United States. Patients planning to receive an oxaliplatin-containing agent or those who had concurrent radiotherapy were excluded from the study. Subjects who reported opioid analgesia dependency at the time of screening were also excluded. Patients were randomized in a 2:1 ratio into one of two arms: best supportive oral care with the device (Arm A), or best supportive care only (Arm B).

Patients in Arm A (CMP device) began using the device 10 minutes before the start of chemotherapy infusions in Cycles 1 and 2 and continued throughout the infusion with the device being replaced, with a fresh frozen device, every 30-45 minutes, with optional 5–10-minute breaks between changes. Additionally, 5-minute breaks every 15 minutes were allowed should patients not tolerate the device continuously for the full 30-45 minutes. For patients receiving continuous chemotherapy infusions at home, a fresh, frozen device was used at least four times a day, for 30-45 minutes each time.

In addition to utilizing the device during infusion, the subjects used a fresh, frozen device, at home, twice a day for 30 minutes each time, on the day of infusion and then for the next 5 days after infusion.

For chemotherapy regimens involving multiple infusions within a single cycle, subjects were instructed to use the device on each infusion day as they would on Day 1.

Actual usage times were recorded by the patients in a daily diary. All study patients were instructed to complete a daily diary for the first 14 days of Cycles 1 and 2 to document device use for patients in Arm A (CMP device) and oral pain using a categorical Oral Mucositis Symptom Assessment scale (OMSA) and analgesic use for all study participants.

Device Description

The device was developed as a reusable, self-contained cryotherapy delivery unit consisting of an inner chamber prefilled with filtered water, an outer chamber prefilled with saline, and a mouthpiece in one of two sizes which is fitted with breathing tubes (large dimensions: 57.65 mm x 53.34 mm; small dimensions: 45.97 mm x 42.42 mm). The shaft of the device is the same and only the mouth portion differs in size. The device is made of medical-grade silicone, water, and a proprietary saline solution and may be reused for up to one year (Figure 1). Subjects were instructed on device use.

The device was granted FDA marketing clearance in early 2024.

Oral Pain and Analgesic Assessment

Analgesic use or nonuse was recorded at the time of scoring and then daily for the first 14 days of chemotherapy cycles 1 and 2 using a diary. A binary sceoring system was used where 0 indicated nonuse and 1 confirmed analgesic use. Medication type was reported in instances of confirmed use and then stratified into three categories: rescue medication, non-opioid analgesics, and opioids.

Rescue medication was defined as a topically administered palliative medication such as Magic Mouthwash, lozenges, Orajel, or lidocaine. Non-opioid analgesics were orally administered over-the-counter medications such as acetaminophen or ibuprofen. Opioids included oxycodone, hydrocodone, and tramadol.

Analysis

Descriptive statistical methods were used to summarize the data including number of subjects (n), mean, median, standard deviation (SD), standard error of the mean (SEM), and frequencies and percentages for categorical data. A chi-square analysis was used to determine statistical significance between arms and cycles.

Findings were evaluated for two populations, intent-to-treat (ITT), and the per-protocol (PP). The intent to treat (ITT) population included all randomized patients who completed at least one assessment score (Arm A, CMP device =97; Arm B, control = 50) during days 1-14 of each of the first two chemotherapy cycles.

The per protocol (PP) population included only those patients who had completed the pain and medication diary every day for the first 14 days of cycles 1 and 2 of chemotherapy. For the purposes of analysis, Cycles 1 and 2 were treated independently.

Results

Demographics

One hundred and sixty-four (164) patients were randomized to either Arm A (CMP device) (n=110) or Arm B (control) (n=54) arms. Study arms were equivalent for sex, age and race (Table 1). Both arms were overwhelmingly female (device 73.6% vs 83.3%) and had comparable median ages (device 63.5 vs 57.5), Within the

device arm, subjects mostly identified as White (64.5%) followed by Other (15.5%), Black (12.7%) and Asian (5.5%). The control arm followed a similar distribution with most subjects identifying as White (57.4%), followed by Black (22.2%), Other (14.8%), and Asian (5.6%).

Primary tumor location (Table 2) was predominantly breast within both arms, Arm A (CMP device) = 52.7% vs. Arm B (control)= 61.1%, followed by colon (10% vs. 7.4%).

	Arm A (All Sites)	**Arm B (All Sites)**
	n=110 [%]	**n=54 [%]**
Male	29 [26.4]	9 [16.7]
Female	81 [73.6]	45 [83.3]
White	78 [70.9]	33 [61.1]
Black	14 [12.7]	13 [24.1]
Asian	6 [5.5]	2 [3.7]
Latino	3 [2.7]	2 [3.7]
Unknown/Not Reported	9 [8.2]	3 [5.6]
More than 1	0 [0]	1 [1.9]
Median Age	63.5	57.5
Mean Age	60.8	57.3
Breast	58 [52.7]	33 [61.1]
Colon	11 [10]	4 [7.4]
Epithelial Cancer	1 [0.9]	0 [0]
Esophageal	0 [0]	1 [1.9]
Gastrointestinal, Hepatobiliary	3 [2.7]	0 [0]
Hodgkin's Lymphoma	6 [5.5]	2 [3.7]
Lymphoma	4 [3.6]	2 [3.7]
Malignant neoplasm of endometrium	1 [0.9]	0 [0]
Posterior Pharynx	1 [0.9]	0 [0]
Multiple Myeloma	1 [0.9]	0 [0]
Ovarian	2 [1.8]	3 [5.6]
Testicular	1 [0.9]	0 [0]
Sarcoma	0 [0]	1 [0.9]
Carcinoma	7 [6.4]	5 [9.3]
Lung	2 [1.8]	2 [3.7]
Leukemia	1 [0.9]	1 [1.9]
Other	11 [10]	0 [0]

Table 1: Patient demographics for intent-to-treat population.

Treatment Days	**ITT Population**			**Per Protocol (PP) Population**		
	Arm A- CMP	**Arm B**	**p-value**	**Arm A-CMP**	**Arm B**	**p-value**
Cycle 1	(n=1041)	(n=638)		(n=714)	(n=504)	
Rescue Medication	1.2% (13/1041)	0.9% (6/638)	0.6	1.4% (10/714)	0.60% (3/504)	0.2
Non-Opioid Analgesics	1.3% (14/1041)	4.1% (26/638)	**<0.001**	1.4% (10/714)	3.8% (19/504)	**0.007**
Opioids	0	2.7% (17/638)	**<0.001**	0	2.8% (14/504)	**<0.001**
Cycle 2	(n=842)	(n=577)		(n=644)	(n=434)	
Rescue Medication	0.10% (1/842)	1.6% (9/577)	**0.001**	0.20% (1/644)	1.60% (7/434)	**0.006**
Non-Opioid Analgesics	0.40% (3/842)	1.6% (9/577)	**0.01**	0.30% (2/644)	2.10% (9/434)	**0.008**
Opioids	0.10% (1/842)	2.9% (17/577)	**<0.001**	0	3.9% (17/434)	**<0.001**
Combined Cycles 1+2	(n=1883)	(n=1215)		(n=1358)	(n=938)	
Rescue Medication	0.7% (14/1883)	1.2% (15/1215)	0.1	0.8% (11/1358)	1.1% (10/938)	0.6
Non-Opioid Analgesics	0.9% (17/1883)	2.9% (35/1215)	**<0.001**	0.9% (12/1358)	2.9% (27/938)	**<0.001**
Opioids	0.05% (1/1883)	2.8% (34/1215)	**<0.001**	0	3.3% (31/938)	**<0.001**

Table 2: Analgesic use distribution by treatment day.

SUBJECTS	**ITT Population**			**Per Protocol (PP) Population**		
	Arm A- CMP	**Arm B**	**p-value**	**Arm A-CMP**	**Arm B**	**p-value**
Cycle 1	(n=96)	(n=50)		(n=51)	(n=36)	
Rescue Medication	2.1% (2/96)	4% (2/50)	0.6	2% (1/51)	2.8% (1/36)	1
Non-Opioid Analgesics	7.3% (7/96)	14% (7/50)	0.2	7.8% (4/51)	13.9% (5/36)	0.4
Opioids	0	4% (2/50)	0.1	0	2.8% (1/36)	0.4
Cycle 2	(n=68)	(n=44)		(n=46)	(n=31)	
Rescue Medication	1.5% (1/68)	6.8% (3/44)	0.2	2.2% (1/46)	6.5% (2/31)	0.5
Non-Opioid Analgesics	2.9% (2/68)	11.4% (5/44)	0.1	2.2% (1/46)	16.1% (5/31)	**0.03**
Opioids	1.5% (1/68)	4.5% (2/44)	0.5	0	6.5% (2/31)	0.1
Combined Cycles 1+2	(n=97)	(n=50)		(n=64)	(n=41)	
Rescue Medication	3.1% (3/97)	8% (4/50)	0.2	3.1% (2/64)	7.3% (3/41)	0.3
Non-Opioid Analgesics	9.3% (9/97)	16% (8/50)	0.2	7.8% (5/64)	19.5% (8/41)	0.1
Opioids	1% (1/97)	4% (2/50)	0.2	0	4.9% (2/41)	0.1

Table 3: Analgesic use distribution by subject.

Analgesic Use

By Patient

Use of the device was associated with less use of analgesics at each of the three levels evaluated.

Patients in the ITT population using the device reported significantly less analgesic use in Cycles 1 and 2, Arm A (CMP device) 11.3% vs Arm B (control) 26%; p=0.03, as did patients in the PP population, Arm A (CMP device) 9.4% vs Arm B (control) 29.3%; p=0.01.

When stratified by chemotherapy cycle, within the ITT population analgesic use incidence by subject was 9.4% in Arm A (CMP device) and 22% in Arm B (control) patients (p=0.04) during Cycle 1. In Cycle 2, the percentage of analgesic use by subject within the ITT population was 4.4% for Arm A (CMP device) and 18.0% for Arm B (control) (p=0.02).

Within the PP population, analgesic incidence by patient was 9.8% in Arm A (CMP device) and 22.2% in Arm B (control) during Cycle 1 (p=0.1). In Cycle 2, the difference was more pronounced as analgesics were used by 2.2% of device-using patients compared to 22.6% of patients in the control arm (p=0.002).

By Reported Days

To assess duration of analgesic use, we evaluated the number of study days for each cycle on which patients reported analgesic use (14 days per cycle; Table 2). Patients in Arm A (CMP device) in both the ITT and PP populations reported significantly fewer days of analgesic use compared to Arm B (control). For chemotherapy cycles 1 and 2 of patients in the ITT population, analgesic use was noted on 7.1% of reported days by Arm B (control), compared to 1.8% in Arm A (CMP device); p<0.001. Likewise, a similar finding was observed in the per-protocol population Arm A (CMP device) 1.8% vs Arm B (control) 7.6%; p<0.001.

We further compared analgesic use by reported day for each cancer treatment cycle (Table 2). Analgesic incidence by visit in Cycle 1 in the ITT population was significantly less in patients in Arm A (CMP device); 2.7% vs Arm B (control); 8.00%; p<0.001. Similarly, during Cycle 2, significantly less analgesic incidence by visit was reported in patients in Arm A (CMP device); 0.6% vs. Arm B (control); 6.1%; p<0.0001.

Among the PP population, analgesic incidence by visit in Cycle 1 was significantly less in patients using the device Arm A (CMP device); 2.9% compared to Arm B (control); 7.5%; p<0.001. In Cycle 2, analgesic incidence by visit decreased in patients in Arm A (CMP device); 0.5%, whereas analgesic incidence by visit slightly increased in the control group Arm B (control); 7.6%; p<0.001.

Analgesic use by type

By Subject

During Cycle 1, no device-using patients in either the ITT or PP cohorts (Arm A, CMP device) reported using opioids (Table 3).

Among the ITT population, 2.1% and 7.3% of patients using the device reported rescue medication and non-opioid analgesic use, respectively. Higher incidences of analgesic use during Cycle 1 were observed in the Arm B (control) with 4% compared to Arm A (CMP device); p=0.6 of patients reporting rescue medication and opioid use and 14% compared to Arm A (CMP device); p=0.2 of patients reporting non-opioid analgesics. Within the PP population control group, incidence of rescue medication use, non-opioid analgesic use, and opioid use by subject was 2.8%, 13.9%, and 2.8%, respectively, during Cycle 1. In patients using the device, Arm A (CMP device) the incidence of rescue medication use by subject was 2.0% (p=1.0) and non-opioid analgesics use 7.8% (p=0.4) in Cycle 1 (Table 3).

Among the ITT population, the percentage of device-using patients Arm A (CMP device) who used rescue medication, non-opioid analgesics, or opioids during Cycle 2 was 1.5%, 2.9%, and 1.5%, respectively (Table 3) compared to the control group (Arm B) in which rescue medication, non-opioid analgesic, or opioid use during Cycle 2 was 6.80% (p=0.2), 11.4% (p=0.1), and 4.5% (p=0.5), respectively (Table 3). Similar trends were observed among the PP population with 0% of Arm A (CMP Device) patients taking opioids and 2.2% taking rescue medication and non-opioid analgesics during Cycle 2 (Table 3). The percentage of Arm B (control) patients using rescue medication and opioids within the PP population during Cycle 2 was 6.5% (p=0.5; p=0.1), and 16.1% (p=0.03) used non-opioid analgesics (Table 3).

Comparing analgesic use type for both Cycles 1 and 2 between study cohorts, within the ITT population, 3.1%, 9.3%, and 1.0% of patients using the device (Arm A, CMP device) used rescue medication, non-opioid analgesics, and opioids, respectively, whereas a higher intensity of analgesics were used by controls (Arm B): 8.0% (p=0.2), 16.0% (p=0.2), and 4.0% (p=0.2) of patients reporting rescue medication, non-opioid analgesics, and opioid use, respectively. Among device-using patients (Arm A, CMP device) in the PP population, no patients reported opioid use, and 3.1% and 7.8% reported rescue medication and non-opioid analgesics use. Consistent with the ITT population, control patients (Arm B) within the PP population demonstrated higher, but not significantly different rates of rescue medication, non-opioid analgesic, and opioid use by subject. Specifically, the percentage of patients using rescue medication, non-opioid analgesics, and opioids was 7.3% (p=0.3), 19.5% (p=0.1), and 4.9% (p=0.1), respectively.

By reported day (Table 2).

To assess differences in duration of analgesic use between cohorts, we evaluated the frequency of analgesic-associated days during the first 14 days of both chemotherapy cycles. During Cycle 1, no days of opioid use were reported by patients (ITT cohort) in Arm A (CMP device), but 1.2% and 1.3% reported days were associated with the use of rescue medication and non-opioid analgesics, respectively. In Arm B (control), opioid use was 2.7% ($p<0.001$) whereas the incidence of rescue medication and non-opioid analgesics was 0.9% ($p=0.6$) and 4.1% ($p<0.001$), respectively.

In the PP population during Cycle 1, no patient days in Arm A (CMP device) were associated with opioid use whereas 1.4% reported days noted rescue medication and non-opioid analgesics use. In Arm B (control), opioid use was reported in 2.8% of visits (vs Arm A (CMP device); $p<0.001$), rescue medication on 0.6% of study days (vs Arm A (CMP device); $p=0.2$) and non-opioid analgesics was 3.8% (vs Arm A (CMP device); $p=0.007$).

During Cycle 2, device using ITT patients reported using opioids on 0.1% of study days, and 0.1% and 0.4% reported using rescue medication and non-opioid analgesics respectively. In comparison, among patients in Arm B (control), opioid use was 2.9% ($p<0.001$) whereas the incidence of rescue medication and non-opioid analgesics were both 1.6% ($p=0.001$; $p=0.01$).

During Cycle 2, Arm A (CMP device) PP population reported no study days on which opioids were taken. The frequency of rescue medication and non-opioid analgesic use was 0.2% and 0.3%, respectively. On the other hand, among Arm B (control) patients, opioid use was 3.9% ($p<0.001$) whereas the frequency of rescue medication and non-opioid analgesics was 1.6% ($p=0.006$) and 2.1% ($p=0.008$) respectively.

Among patients in the ITT population, opioid use by day (visit) was significantly less for both Cycles 1 and 2 for patients in Arm A (CMP device; 0.05%) compared to patients in the Arm B (control) cohort (2.8%; $p=<0.001$). Likewise, non-opioid analgesic use was also less frequently reported by device-using patients (0.9% vs 2.9% in the control group; $p=<0.001$). Rescue medications were used in 0.7% of reported days in both Cycle 1 and 2 by Arm A (CMP device) patients compared to 1.2% of patients in Arm B (control; not significant). Similar observations were made among patients in the PP population. No visits were associated with opioid use among patients in Arm A (CMP device) versus 3.3% of patient visits in the control Arm B ($p<0.0001$). A significantly lower number of Arm A (CMP device) patient visits were associated with the use of non-opioid analgesics (0.9%) use compared to 2.9% in Arm B (control group), $p=<0.001$. The differences in the frequency of rescue medication were not significant Arm A (CMP device) 0.7% vs Arm B (control) 1.2%.

Discussion

The utility of cryotherapy as an intervention for chemotherapy-associated oral mucositis has been well-established [9-12]. While its effectiveness has been highlighted in mitigating the symptoms of mucosal injury for specific forms of chemotherapy such as bolus 5-FU and high-dose melphalan [11], based on the purported mechanism of action it seems likely that its use may be effective with other cytotoxic agents [9]. While the efficacy of cryotherapy has been confirmed, there are logistical challenges to its current reliance on ice chips as the mechanism of delivery [14]. Aside from the burden of supplying a continuous stream of fresh ice chips to patients, questionable water quality has been identified as a potential ice chip risk [16]. Patient reports of headache, nausea, and chills have negatively impacted ice-chip provided cryotherapy. Finally, the uniformity of cold distribution provided by ice chips has been questioned.

To circumvent these barriers, but still provide effective cold therapy to oral mucosa, the use of intraoral devices has been proposed. One such device utilizes an external source to provide circulating cold water to an intraoral device [16]. Such an approach likely restricts the use of the device to in-clinic and in-hospital settings. Alternatively, extended use of cryotherapy beyond the infusion period has not been routine, and patient enthusiasm for ice chips is mixed at best. The results of this study highlight the potential benefits of using the Chemo Mouthpiece, a novel cryotherapy device, in reducing the need for analgesics in patients experiencing chemotherapy-induced oral mucositis (OM). OM is a severe and common complication for cancer patients undergoing cytotoxic treatments, leading to substantial discomfort, compromised nutrition, and increased infection risks. The burden of pain management often necessitates the use of opioid and non-opioid analgesics, which, although effective, carry significant risks of addiction, adverse side effects, and complications. Therefore, developing interventions that reduce reliance on these medications without compromising pain management is imperative.

Our study demonstrated that the use of the Chemo Mouthpiece was associated with a significant reduction in both the incidence and frequency of analgesic use, particularly opioids, across two chemotherapy cycles. This finding was consistent in both the intent-to-treat (ITT) and per-protocol (PP) populations. In the ITT population, the percentage of patients using any form of analgesics, including rescue medication and opioids, was markedly lower in the Chemo Mouthpiece group compared to the control group. Similarly, the per-visit analysis (duration) also showed significant reductions in the use of analgesics, further supporting the efficacy of the device in managing mucositis induced pain.

The importance of reducing opioid use cannot be overstated, particularly in light of the known risks associated with long-

term use [17-18]. Patients using the Chemo Mouthpiece reported significantly less opioid use than the control group, particularly during the second chemotherapy cycle. This reduction in opioid use is a key finding, as it suggests that cryotherapy, delivered through the Chemo Mouthpiece, can provide adequate pain relief without the need for heavy reliance on opioids.

In addition to reducing opioid use, the Chemo Mouthpiece also led to a decrease in the use of non-opioid analgesics and rescue medications. This is significant because non-opioid analgesics, while generally considered safer, can still pose risks when used excessively, such as gastrointestinal bleeding or kidney damage [19-20]. The ability of the Chemo Mouthpiece to mitigate pain and reduce the overall analgesic burden confirms the effectiveness of cryotherapy as adjunct in the management of mucositis and demonstrates the utility of a self-contained device as a consistent means of administration.

Despite the promising results, there are some limitations to consider. The study, while randomized, could not be blinded and therefore open to the placebo effect. Secondly, the study consisted primarily of female patients, and the primary tumor locations were overwhelmingly breast and colon cancers. While these demographics reflect common cancer populations, future studies should evaluate the device's effectiveness across a more diverse patient population and in other cancer types.

Conclusion

Overall, this study provides strong evidence that the Chemo Mouthpiece effectively reduced the need for all forms of analgesic use to manage chemotherapy-induced oral mucositis-associated pain. By offering a non-pharmacological alternative for pain management, the device not only improves patient comfort but also aligns with broader healthcare goals of minimizing drug related complications and improving the overall quality of life for cancer patients. As the treatment landscape for oral mucositis evolves, integrating innovative devices such as the Chemo Mouthpiece into standard care protocols could significantly reduce the burden of analgesic use and enhance patient outcomes. Further studies are warranted to confirm these findings in larger, more diverse populations and to explore long-term benefits associated with reduced analgesic use.

Ethics Approval Statement

The protocol for this study was approved by a suitably constituted Ethics Committee (Institutional Review Board or Regional Institutional Review Board) for each institution and conforms to the provisions of the Declaration of Helsinki.

All subjects were consented prior to study start.

Funding: This trial was funded by ChemoMouthpiece, LLC.

Data Availability Statement: Data generated during this study are available from the corresponding author on reasonable request.

Conflict of Interest: RZ is a consultant for Mirati Therapeutics, Flatiron and Bristol-Myers Squibb (BMS) and has received research and travel support from ChemoMouthpiece, LLC; VD participates in a Speaker Bureau for BMS/ Regeneron and has equity in BMS; FJ is an employee of ChemoMouthpiece; SS is an employee of Biomodels, LLC and Primary Endpoint Solutions, LLC.

Author Contributions: VD, KC, RV, KW, IJ, RZ: study execution and data collection, editing manuscript. SS: study concept, design, data analysis, preparation of initial manuscript and editing. FJ: study concept, overall management, funding, editing.

References

1) Curra M, Junior LAVS, Martins MD, Santos PSDS (2018) Chemotherapy protocols and incidence of oral mucositis. An integrative review. Einstein (Sao Paulo) 16:eRW4007.

2) Brown TJ, Gupta A (2020) Management of Cancer Therapy-Associated Oral Mucositis. JCO Oncol Pract 16:103-109.

3) Sonis ST (2013) Oral mucositis in head and neck cancer: risk, biology, and management. Am Soc Clin Oncol Educ Book 2013.

4) Mavić MP, Šeparović R, Vuger AT, Vazdar L (2021) Difference in Estimation of Side Effects of Chemotherapy between Physicians and Patients with Early-Stage Breast Cancer: The Use of Patient Reported Outcomes (PROs) in the Evaluation of Toxicity in Everyday Clinical Practice. Cancers (Basel) 13:5922.

5) Murdock JL, Reeves DJ (2020) Chemotherapy-induced oral mucositis management: A retrospective analysis of MuGard, Caphosol, and standard supportive care measures. J Oncol Pharm Pract 26:521-528.

6) Immonen E, Aine L, Nikkilä A, Parikka M, Grönroos M, et al. (2020) Randomized controlled and double-blinded study of Caphosol versus saline oral rinses in pediatric patients with cancer. Pediatr Blood Cancer. Pediatr Blood Cancer 67:e28520.

7) Nugent M, Bryant V, Butcher C, Fisher H, Gill S, et al. (2022) Photobiomodulation in the management of oral mucositis for adult head and neck cancer patients receiving irradiation: the LiTEFORM RCT. Health Technol Assess 26:1-172.

8) Legouté F, Bensadoun RJ, Seegers V, Pointreau Y, Caron D, et al. (2019) Low-level laser therapy in treatment of chemoradiotherapy-induced mucositis in head and neck cancer: results of a randomised, triple blind, multicentre phase III trial. Radiat Oncol 14:83.

9) Al-Rudayni AHM, Gopinath D, Maharajan MK, Veettil SK, Menon RK, et al. (2021) Efficacy of Oral Cryotherapy in the Prevention of Oral Mucositis Associated with Cancer Chemotherapy: Systematic Review with Meta-Analysis and Trial Sequential Analysis. Curr Oncol 28:2852-2867.

10) Riley P, Glenny AM, Worthington HV, Littlewood A, Clarkson JE, et al. (2015) Interventions for preventing oral mucositis in patients with cancer receiving treatment: oral cryotherapy. Cochrane Database Syst Rev 2015.

11) Correa MEP, Cheng KKF, Chiang K, Kandwal A, Loprinzi CL, et al. (2020) Systematic review of oral cryotherapy for the management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer 28:2449-2456.

12) Riley P, Cabe MGM, Glenny AM (2016) Oral Cryotherapy for Preventing Oral Mucositis in Patients Receiving Cancer Treatment. JAMA Oncol 2:1365-1366.

13) Kadakia KC, Rozell SA, Butala AA, Loprinzi CL (2014) Supportive cryotherapy: a review from head to toe. J Pain Symptom Manage 47:1100-15.

14) Ibrahim A, Camci E, Khairallah L, Jontell M, Walladbegi J (2023) Cryopreventive temperatures prior to chemotherapy. Med Oncol 40:148.

15) Zuniga R, Dembla V, Alam N (2024) Multi-Institutional, randomized, controlled trial to assess the efficacy and tolerability of a reusable, self-contained cryotherapy delivery device. Support Care in Cancer 2024.

16) Walladbegi J, Gellerstedt M, Svanberg A, Jontell M (2017) Innovative intraoral cooling device better tolerated and equally effective as ice cooling. Cancer Chemother Pharmacol 80:965-972.

17) Carmona-Bayonas A, Jiménez-Fonseca P, Castañón E, Ramchandani-Vaswani A, Sánchez-Bayona R, et al. (2017) Chronic opioid therapy in long-term cancer survivors. Clin Transl Oncol 19:236-250.

18) Abdel Shaheed C, Hayes C, Maher CG, Ballantyne JC, Underwood M, et al. (2024) Opioid analgesics for nociceptive cancer pain: A comprehensive review. CA Cancer J Clin 74:286-313.

19) Onyeakusi NE, Gbadamosi SO, Mukhtar F, Orji C, Ugwuowo U, et al. (2019) Association between long-term NSAID use and opioid abuse among patients with breast cancer. Cancer Treat Res Commun 21:100156.

20) Bindu S, Mazumder S, Bandyopadhyay U (2020) Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol 180:114147.