ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

Cooral System for the Prevention of Oral Mucositis

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Summary of Key Points

- Oral mucositis (OM) is a severely debilitating condition secondary to cancer therapies such as chemo- and radiotherapy, leading to inflammation of the oral mucosa.
- Oral cryotherapy, such as ice chips, are recommended to prevent OM in patients receiving chemotherapy. However, it is limited by patient discomfort, poor tolerance, non-uniform cooling effects and fluctuations in temperature across the oral cavity.
- The Cooral System (BrainCool AB) involves a single-use intraoral cooling device in a closed-loop circulatory system, with cooled solution delivered by a portable thermostat unit to evenly distribute the hypothermic medium to the oral mucosa. Compared to ice chips, it provides uniform cooling at a controlled temperature, and may improve patient's tolerance and compliance.
- Results from a randomised controlled trial (n=172) that included patients with multiple myeloma and lymphoma scheduled to receive high-dose chemotherapy prior to autologous hematopoietic stem cell transplantation found that the Cooral system was well tolerated and had a relatively good safety profile compared to ice chips.
    - No serious adverse events were reported.
    - Compared to ice chips, the Cooral system led to significantly lower frequency of oral numbness, teeth hypersensitivity and nausea with significantly higher number of swallowing difficulties, poor fit and rubbing discomfort due to the design of the device.
    - The Cooral system was significantly better tolerated than ice chips in the overall cohort.
- In terms of effectiveness, the Cooral system and ice chips were generally comparable in terms of patient outcomes, including chemotherapy-induced OM severity, oral pain, quality-of-life and days of hospitalisation.
- Of note, the study appeared to be underpowered for its primary endpoint (i.e., OM severity) and was also limited by the applicability of the findings to other population groups scheduled to receive chemotherapy.
- The Cooral system is unlikely to be cost effective over ice chips given the similar treatment efficacy and additional cost incurred.
- There are no implementation barriers anticipated to adopt the technology locally.
- At present, there are two ongoing small scale feasibility studies investigating the use of the Cooral system in preventing OM in patients with solid tumours.

I. Background

Oral mucositis (OM) is a severely debilitating condition that involves inflammation of the oral mucosa.[1] It is a frequent complication in patients who receive radiation therapy to the head and neck, systemic chemotherapeutic agents for solid tumours or lymphoma, or high-dose myeloablative chemotherapy prior to hematopoietic stem cell transplantation (HSCT).[1] More recently, the manifestation of OM was also observed in patients treated with targeted and immunologically-based agents.[2] Clinically, OM is presented as erythema, edema and ulcerations within the oral mucosa.[1]

In the United States, it was estimated that around 400,000 patients suffer from OM each year.[3] The incidence of OM varies between different chemotherapeutic agents and its dose,

affecting about 20% to 40% of patients receiving chemotherapy for solid tumours, 80% of patients receiving high-dose chemotherapy prior to HSCT and in almost all patients receiving radiotherapy for head and neck cancer.[3] OM presents substantial morbidity, with severe pain from the ulcerative lesions that can further compromise food intake, oral hygiene and quality-of-life (QoL).[3] These lesions may also provide a route for potentially life-threatening sepsis, especially in immunocompromised patients.[3] OM may also impact patient prognosis from undesirable dose reduction or a break in cancer therapy.[3,4] Besides the high disease burden, the economic impact of OM is considerably high, where a single-point increase in OM severity score as assessed by the OM Assessment Scale (OMAS; score of 0 [none] to 5 [severe]) was found to be associated with additional 2.6 hospital days and $25,000 in hospital charges.[3]

Oral cryotherapy, such as ice chips, is conventionally used as a preventive measure of OM owing to vasoconstriction that limits delivery of chemotherapy drugs to the oral mucosa.[3] However, it is limited by patient discomfort, poor tolerance, non-uniform cooling effects and fluctuations in temperature across the oral cavity.[5] It is also important to ensure that good quality water is used for ice chips to prevent microorganism contamination which may compromise the health of an immunocompromised patient.[6]

II. Technology

The Cooral System (BrainCool AB) is a continuous flow thermoregulator device that serves as a prophylactic strategy for the prevention of OM. It involves an attachable single-use intraoral cooling device in a closed-looped circulatory system, with cooled solution delivered by a portable thermostat unit to evenly distribute the hypothermic medium to the oral mucosa (Figure 1).

Figure 1: The Cooral System. Illustration of the intraoral cooling device (**left**) and the thermostat cooling unit (**right**). Image adapted from Mahdi et al. (2021)[6].

Compared to ice chips, the Cooral system has the potential to offer a more tolerable cryotherapy solution that may improve patient's adherence and maintain a controlled temperature throughout the chemotherapy session with uniform distribution of cooling. However, it should be noted that since the cooling is temporary, cryotherapy is suited for cytotoxic regimens that are delivered over a short period of time or those with a short half-life.[7]

III. Regulatory and Subsidy Status

The Cooral System was granted the Breakthrough Device Designation by the US Food and Drug Administration (FDA) in February 2021. It was also CE marked in June 2020.

IV. Stage of Development in Singapore

☒	Yet to emerge	☐	Established
☐	Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used)	☐	Established *but* modification in indication or technique
☐	Nearly established	☐	Established *but* should consider for reassessment (due to perceived no/low value)

V. Treatment Pathway

Guideline jointly published by the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) reported various preventive and treatment interventions for OM management, such as basic oral care, photobiomodulation and cryotherapy.[7] The overall guideline recommendations made by MASCC/ISOO were summarised in Table 1 for patients receiving chemo- or radiotherapy. Based on the guideline, oral cryotherapy is recommended for the prevention of OM in two clinical situations, both of which involves patients receiving systemic chemotherapy.[7]

Table 1: Summary of MASCC/ISOO recommendations[7] for the management of OM

Patients receiving systemic chemotherapy
• Oral cryotherapy is recommended to prevent OM in patients receiving bolus fluorouracil or patients undergoing autologous HSCT when conditioning with high-dose melphalan • Thirty minutes of oral cryotherapy is recommended to prevent OM in patients receiving bolus 5-FU CT during the infusion of the CT • Keratinocyte growth factor-1 is recommended to prevent OM in patients with hematologic cancer undergoing autologous HSCT with a conditioning regimen that includes high-dose CT and TBI • Intraoral photobiomodulation therapy using low-level laser therapy is recommended to prevent OM in adult patients receiving HSCT conditioned with high-dose CT, with or without TBI
Patients receiving head and neck radiotherapy
• Benzydamine mouthwash is recommended to prevent OM in patients with head and neck cancer receiving a moderate dose of RT (<50 Gy) • Intraoral photobiomodulation therapy using low-level laser therapy is recommended to prevent OM in adult patients receiving RT to the head and neck, with or without concurrent CT
Abbreviations: 5-FU, 5-fluorouracil; CT, chemotherapy; HSCT, hematopoietic stem cell transplantation; OM, oral mucositis; RT, radiotherapy; TBI, total body irradiation.

The introduction of the Cooral System is not expected to disrupt current treatment pathway, but rather provide an alternative cryotherapy option for patients who are receiving systemic chemotherapy that may potentially increase tolerance and compliance.

VI. Summary of Evidence

The assessment was conducted based on the Population, Intervention, Comparison and Outcome (PICO) criteria presented in Table 2. Based on literature search conducted in PubMed and Embase, one randomised controlled trial (RCT; n=172)[8] was included. Briefly, it compared the Cooral system with ice chips in patients with multiple myeloma or lymphoma scheduled to receive high-dose chemotherapy conditioning prior to autologous HSCT. Another study[9] involving 20 healthy volunteers served as supporting evidence. The evidence base, the inclusion and exclusion criteria were listed in Table A1 (Appendix A) while the study design and characteristics were presented in Table A2 (Appendix A).

Table 2: Summary of PICO criteria

Population	Patients scheduled to receive chemotherapy
Intervention	Cooral system
Comparison	Conventional oral cryotherapy, such as ice chip or cold water
Outcome	Safety, clinical and cost effectiveness

Safety

Overall, the Cooral system was found to have a relatively good safety profile in comparison with ice chips, with no serious adverse events (SAEs) reported.[8] In terms of adverse events (AEs), when compared with ice chips, the Cooral system led to significantly less frequent oral numbness (2.5% *vs.* 10.3%, p=0.041), teeth hypersensitivity (6.3% *vs.* 19.5%, p=0.011) and nausea (3.8% *vs.* 12.6%, p=0.038; Table 3).[8] However, there was significantly more swallowing difficulties reported with the Cooral system than ice chips (20% *vs.* 2.3%, p<0.001), which was postulated to be avoidable with a better fitted oral device.[8] The Cooral system also led to other transient AEs unique to the device, such as poor fit and rubbing discomfort which were observed in 20% and 30% of patients who received the device, respectively.[8] These findings corroborated the AEs reported in a study on healthy volunteers (Table B1 in Appendix B).[9]

Table 3: Comparison of safety outcomes between the Cooral system and ice chips

Safety outcomes	Cooral system (n=80)	Ice chips (n=87)	p-value
Serious adverse events, n (%)	0 (0%)	0 (0%)	—
Adverse events			
Chills, n (%)	13 (16.3%)	24 (27.6%)	0.078
Numbness, n (%)	2 (2.5%)	9 (10.3%)	**0.041**
Bad taste, n (%)	2 (2.5%)	6 (6.9%)	0.281
Headache, n (%)	2 (2.5%)	2 (2.3%)	1.000
Teeth hypersensitivity, n (%)	5 (6.3%)	17 (19.5%)	**0.011**
Oral soreness, n (%)	5 (6.3%)	8 (9.2%)	0.478
Nausea, n (%)	3 (3.8%)	11 (12.6%)	**0.038**
Vomiting sensation, n (%)	6 (7.5%)	5 (5.7%)	0.648
Difficulties swallowing, n (%)	16 (20.0%)	2 (2.3%)	**<0.001**
Other discomforts, n (%)	17 (21.3%)	12 (13.8%)	0.204
Poor fit*, n (%)	16 (20.0%)	—	—
Rubbing discomfort*, n (%)	24 (30.0%)	—	—

* Adverse events that were only observed with the Cooral system.

Moreover, patients in the overall study cohort had better degree of tolerability towards the Cooral system than ice chips (odds ratio [OR], 0.274; 95% CI, 0.086 to 0.873; p=0.028), with similar findings in patients in the multiple myeloma subcohort (Table 4).[8] Likewise, the Cooral system was significantly better tolerated than ice chips in healthy volunteers (p=0.0118).[9] However, findings from the lymphoma subcohort demonstrated a lack of significant difference in tolerance between both arms (OR, 0.409; 95% CI, 0.032 to 5.276; p=0.493), although this may be due to the small sample size (n=23; Table 4).[8] Regardless, tolerability would be better assessed with a crossover study design.

Table 4: Tolerability of treatment with the Cooral system and ice chips

Intervention	Patients who reported discomfort*, n/N (%)	OR (95% CI)	p-value
Total cohort (n=167)			
Cooral system (n=80) Ice chips (n=87)	4/80 (5.0%) 14/87 (16.1%)	0.274 (0.086 to 0.873)	**0.028**
Multiple myeloma subcohort (n=144)			
Cooral system (n=68) Ice chips (n=76)	3/68 (4.4%) 12/76 (15.8%)	0.246 (0.066 to 0.914)	**0.036**
Lymphoma subcohort (n=23)			
Cooral system (n=12) Ice chips (n=11)	1/12 (8.3%) 2/11 (18.2%)	0.409 (0.032 to 5.276)	0.493
* Tolerability following each cooling session was assessed using a study-specific questionnaire. Patients who rated "not at all painful" and "slightly painful" were compared as a group with patients who rated the higher levels of "rather painful" and "painful". Abbreviation: OR, odds ratio.			

Effectiveness

The Cooral system was found to be comparable to ice chips in preventing chemotherapy-induced OM. In the overall cohort, there was no significant difference in OM severity (primary endpoint) between patients who received the Cooral system or ice chips as determined by the highest OMAS score assessed during the study period (peak OMAS-total average score, 0.99 ± 1.47 *vs.* 1.24 ± 1.61; p=0.351; Table 5).[8] However, it should be noted that the study was slightly underpowered for its primary endpoint. As indicated in the study, a sample size of at least 90 patients in each arm would provide a power of 80% to detect an average difference of at least 0.42 OMAS-total units, which was not met in the Cooral system (n=84) and ice chips (n=88) arms in the overall cohort analysed.[8]

To further add, OM severity was significantly lower in the Cooral system compared to the ice chips arm in the lymphoma subcohort (peak OMAS-total average score, 1.77 ± 1.59 *vs.* 3.08 ± 1.50; p=0.047), although this difference needs further validation (see Table 5 and Figure B1 in Appendix B).[8]

Table 5: Comparison of oral mucositis severity between the Cooral system and ice chips

Intervention	Peak OMAS-total average score (mean ± S.D.)	p-value
Total cohort (n=172)		
Cooral system (n=84) Ice chips (n=88)	0.99 ± 1.47 1.24 ± 1.61	0.351
Multiple myeloma subcohort (n=146)		

Cooral system Ice chips	0.85 ± 1.41 0.92 ± 1.41	0.734
Lymphoma subcohort (n=26)		
Cooral system Ice chips	1.77 ± 1.59 3.08 ± 1.50	**0.047**
Note: The OMAS is an objective scale that includes the (i) OMAS score of 0 to 3 for ulceration where 0 correspond to healthy oral mucosa, 1≤ 1 cm^2, 2 = 1 to 3 cm^2, 3 ≥ 3 cm^2 ; and the (ii) OMAS score for erythema where 0 correspond to healthy oral mucosa, 1 = mild and 2 = severe. The assessment of the OMAS-ulceration and OMAS-erythema score provides a total average OMAS score (0 to 5). The peak OMAS-total score refers to the highest OM score during the time of care, where each patient was assessed thrice a week from the time of admission until discharge or 28 days after autologous stem cell transplantation. Abbreviation: OM, oral mucositis; OMAS, Oral Mucositis Assessment Scale; S.D., standard deviation.		

Besides OM severity, there was no meaningful difference in the reduction of OM-related oral pain between the Cooral system and ice chips. Using the Numeric Pain Rating Scale (NPRS, 0 to 10 scale), clinically significant discomfort (NPRS ≥3) was reported in 23.2% of patients in the Cooral system arm and 36.8% in the ice chips arm, with no significant difference between both arms (OR, 0.518; 95% CI, 0.25 to 1.072; p=0.076).[8] There were also no statistically significant difference between the two arms for other clinically meaningful outcomes such as patient's QoL, number of hospitalisation days and number of days with total parenteral nutrition.[8]

Cost effectiveness

No studies that reported on the cost effectiveness of the Cooral system were identified. However, given that the Cooral system provides similar treatment efficacy with additional cost incurred compared to ice chips, it is unlikely to be cost effective over ice chips.

Ongoing clinical trials

Aside from haematological cancers, there are ongoing studies investigating the use of the Cooral system in preventing OM in patients with solid tumours. Two small scale feasibility studies were identified from the ScanMedicine database (NIHR Innovation Observatory; Table 6). Of which, the CooRay study was completed in April 2022 and findings from the study may be expected in the near future.

Table 6: Ongoing studies of the Cooral System

Study (Trial ID)	Estimated enrolment	Brief description	Estimated completion date
CooRay (NCT04915599)	10 (actual enrolment)	This feasibility case series conducted in Switzerland investigate the use of the Cooral device to achieve a constant and reproducible cooling of the oral mucosa to prevent oral mucositis in patients undergoing radiotherapy in the head and neck region.	April 2022 (actual completion date)
Feasibility study of Cooral system for oral mucositis in patients receiving chemotherapy (UMIN000034478)	20	This feasibility case series conducted in Japan investigate the use of the Cooral system in patients with breast, gastric, colorectal, oesophageal or gynaecological cancer in preventing oral mucositis in patients receiving chemotherapy.	Not reported

Summary

The Cooral system was found to have a relatively good safety profile compared to ice chips, with a significantly lower frequency of oral numbness, teeth hypersensitivity and nausea. However, the design of the device resulted in a higher number of patients who experienced swallowing difficulties, poor fit and rubbing discomfort. In the overall cohort, there was an improvement in tolerability towards cryotherapy using the Cooral system compared to ice chips, although patient outcomes including OM severity, oral pain scores, hospitalisation duration and QoL generally did not differ significantly between both arms. Limited evidence in the lymphoma subcohort suggests superiority of the Cooral system over ice chips in reducing OM severity, which would require further validation in a larger cohort. Given similar treatment efficacy and additional cost incurred, the Cooral system is unlikely to be cost effective over ice chips.

Of note, the RCT had some limitations. It was slightly underpowered for its primary endpoint in the overall cohort while the applicability of the findings to other population groups scheduled to receive chemotherapy remains unclear, such as patients with solid tumours and paediatric patients.

VII. Estimated Costs

The cost of the Cooral system was not available.

VIII. Implementation Considerations

There were no major adoption barriers anticipated with the introduction of the Cooral system in the local setting.

IX. Concurrent Developments

At present, the Cooral system is the only known cryotherapy device that involves a thermostat unit to enable continuous circulation of hypothermic medium to the oral mucosa. One other cooling device was identified, which involves a frozen tube that fills the oral cavity to prevent OM (Table 7).

Table 7: Similar technology in development

Technology (Manufacturer)	Brief Description	Status
Chemo Mouthpiece (Chemo Mouthpiece, LLC)	It consists of an inner chamber filled with pure water and an outer chamber filled with saltwater. When the Chemo Mouthpiece is put in a standard freezer, the inner pure water chamber will freeze solid, but the outer saltwater chamber will not. The outer saltwater chamber stays ice cold, which allows the mouthpiece to cool a patient's oral cavity	Granted FDA BDD and currently investigated in a randomised controlled trial
Abbreviation: BDD, breakthrough device designation; FDA, US Food and Drug Administration.		

X. Additional Information

The study was funded by BrainCool AB, with some of the authors receiving a personal or consultation fee from the company.

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Appendix

Appendix A: Studies included and study design.

Table A1: List of included studies.

Type of study	Number of study included
Randomised controlled trial	1
Note: 1. Inclusion criteria a. Studies that fulfil the PICO criteria listed in Table 1. 2. Exclusion criteria a. Studies only available in the abstract form.	

Table A2: Study design and characteristic of the included study

Study design	Randomised controlled trial
N	172
Population	Patients ≥18 years old confirmed with multiple myeloma or lymphoma and scheduled to receive high-dose conditioning chemotherapy prior to autologous stem cell transplantation
Intervention	Cooral system. A water temperature of 8°C (±2°C) was used as the default setting throughout the study
Comparison	Ice chips manufactured from tap water (-0.5°C) Patients were instructed to insert an ounce of ice and move the ice chip around in the mouth
Outcomes	Primary endpoint: • OM, defined as peak OMAS-total Secondary endpoints: • Degree of tolerability • Patient-reported oral pain defined as NPRS ≥3 Tertiary endpoints: • Quality-of-life at admission and discharge, using FACT-G (version 4) • Number of days with total parenteral nutrition • Number of hospital days • Total dose of opioid analgesics converted to morphine • Peak C-reactive protein • Maximum weight loss, defined as initial value minus the lowest value (kg) • Number of days from transplantation to bone marrow engraftment, defined as ANC > 1.0 x 10^9 cells/L • Maximum drop for s-Albumin, defined as highest value minus the initial value (g/L) • Maximum temperature increase, defined as highest value minus the initial value °C
Abbreviations: FACT-G, Functional assessment of cancer therapy – general; OM, oral mucositis; OMAS, Oral Mucositis Assessment Scale.	

Appendix B: Supplementary tables and figures of included studies.

Table B1: Adverse events observed in healthy volunteers

Safety outcome	Ice chips, n	Cooral system, n
Adverse event		
Cold	12	3
Numbness	11	3
Bad taste	3	1
Headache	2	0
Teeth sensations	8	2
Pain	5	3
Poor fit*	0	7
Nausea	4	1
Vomiting sensation	1	3
Difficulties in swallowing	0	15
Rubbing discomfort*	2†	12

* Adverse events only observed for the Cooral system.
† Reported as 'other comments'.
Table adapted from Walladbegi et al. (2017)[9].

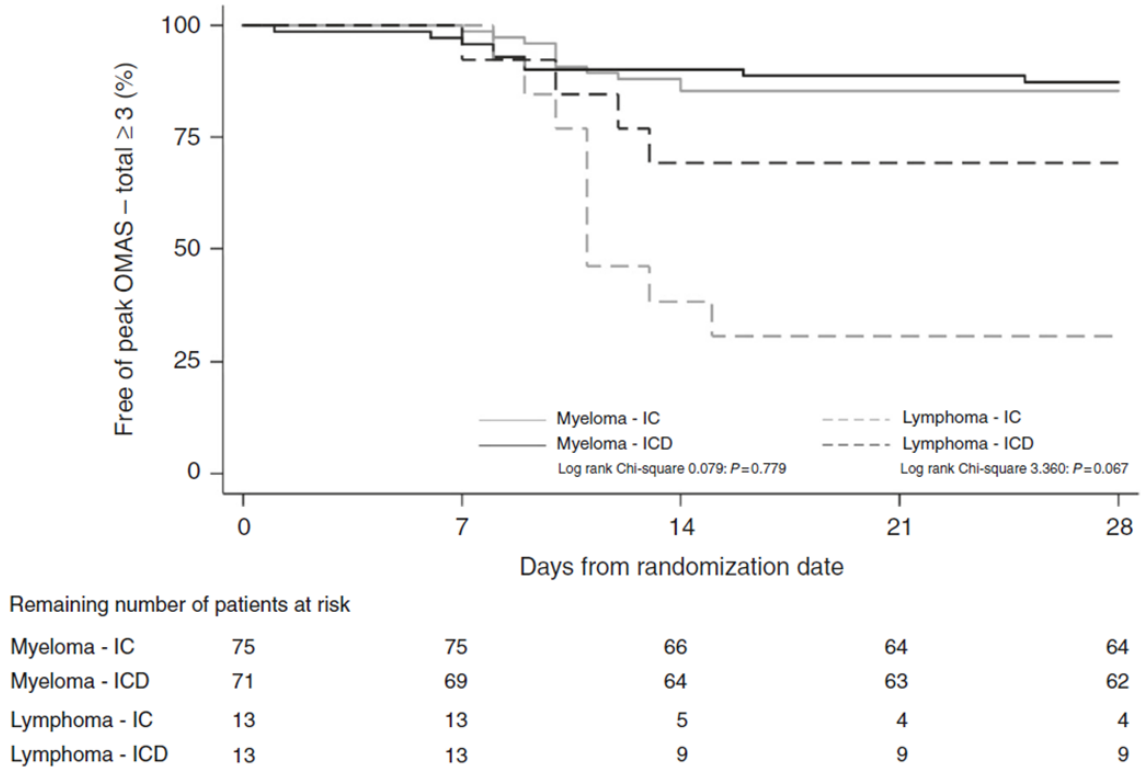

Figure B1: Kaplan Meier curve for patients with severe oral mucositis. The number of patients with severe oral mucositis (peak OMAS-total ≥3), following conditioning with chemotherapy. Image adapted from Walladbegi et al. (2022)[8].