APPENDIX 6: RANDOMIZED CONTROLLED TRIALS OF CRYOTHERAPY FOR THE PREVENTION OF ORAL MUCOSITIS IN ADULT AND PEDIATRIC PATIENTS RECEIVING TREATMENT FOR CANCER OR UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION – OUTCOMES

First Author (Year)	COMPARISONS	OUTCOMES				
		Number Received Intervention Group 1	Number Received Intervention Group 2	Description of Main Mucositis Findings	Description of Main Pain Findings	Description of Adverse Events
Katranci (2012) [1]	Cryotherapy versus no cryotherapy	30	30	For day 21, 1/30 in cryotherapy arm vs 6/30 in control group had severe mucositis	Not measured	No toxicity and no discomfort
Salvador (2012) [2]	Cryotherapy versus no cryotherapy	23	22	Overall mean (SE) of oral mucositis severity for the cryotherapy arm significantly lower than that for the control group: 0.43 (0.12) vs 1.14 (0.12); P<0.001 on a 0-4 scale	Overall mean (SE) mucositis-related pain score for the cryotherapy arm significantly lower than that for the control group: 0.30 (0.23) vs 1.64 (0.24); P < 0.001 on a 0-10 scale	Four participants experienced teeth sensitivity and complained of chills during cryotherapy, did not deter completion of therapy
Sorensen (2008) [3]	Cryotherapy versus oral rinse	67	66	Frequency of grade 3 or 4 oral mucositis was 10% in cryotherapy arm and 32% in saline rinse control group (P<0.005)	Not reported	No significant differences with respect to compliance or to side effects such as headache or taste disturbances. No effects on teeth
Svanberg (2007) [4] (companion papers: [5], [6])	Cryotherapy versus no cryotherapy	39	39	Auto: Cryotherapy significantly lower mucositis score on day 10 (1.6±1.9 vs 4.3±5.7; P=0.042) Allo: Cryotherapy significantly lower mucositis score on day 16 (3.7±1.8 vs 11.6±6.8; P=0.021)	No significant difference in pain between cryotherapy and control arms for either auto or allo group	Seven patients (18%) found oral cryotherapy unpleasant, and among those, four (10%) found it very unpleasant, mostly because of shooting pain from teeth
Gori (2007) [7]	Cryotherapy versus no cryotherapy	62	60	Incidence of grade 3–4 oral mucositis comparable (47% in cryotherapy arm vs. 53% in control group; P=0.46). Maximum mean mucositis score comparable (1.98±1.12 in cryotherapy arm vs 2.13±1.24 in control group; P=0.56). Duration of mucositis among patients with either grade 3–4 or grade 2–4 mucositis was comparable	Not reported	Not reported
Papadeas (2007) [8]	Cryotherapy versus no cryotherapy	36	40	Percentage patients free from oral toxicity higher in cryotherapy arm (P<0.01) according to physicians' evaluation in all three chemotherapy cycles	Not reported	Mouth numbness or headache (n=6); did not deter cryotherapy
Lilleby (2006) [9]	Cryotherapy versus warm saline rinses	21	19	Cryotherapy group experienced less grade 3–4 mucositis than normal saline group (14 vs 74%, P=0.0005). Average number of days with grade 3 mucositis: 0.5 in cryotherapy group vs 4.6 in normal saline group (P=0.0001). Mean of average daily mucositis scores for cryotherapy vs. normal saline groups: 0.41 vs 1.06; P=0.0005	Mean of average mouth pain scores 2.7 for normal saline vs 0.6 for cryotherapy groups (P=0.003)	Some patients complained of coldness and stopped using ice chips
Baydar (2005) [10]	Cryotherapy versus no cryotherapy	45	54	Development of mucositis correlated only with cryotherapy in logistic regression: OR=11.5; 95% CI=3.2 to 41.9; P=0.001	Not reported	No local or systemic side effects due to cryotherapy

First Author (Year)	**COMPARISONS**	**OUTCOMES**				
		Number Received Intervention Group 1	Number Received Intervention Group 2	Description of Main Mucositis Findings	Description of Main Pain Findings	Description of Adverse Events
Karagozoglu (2005) [11]	Cryotherapy versus no cryotherapy	30	30	Patient-judged: Rate of mucositis 36.7% with cryotherapy and 90.0% in control group; P<0.05. Physician-judged: Rate of mucositis 10.0% with cryotherapy and 50.0% in control group; P<0.05	Not reported	Not reported
Nikoletti (2005) [12]	Cryotherapy versus no cryotherapy	NR	NR	Standard care vs cryotherapy: OAG: OR 3.26, 95% CI 1.55 to 6.90; P=0.002. WCCNR: OR 3.23, 95% CI 1.19 to 9.09; P=0.021	Cryotherapy more effective than standard care in reducing average reported pain (P=0.009)	Nausea, sensitivity and headache with cryotherapy (n = 5)
Cascinu (1994) [13]	Cryotherapy versus no cryotherapy	44	40	Mucositis significantly reduced by cryotherapy with first cycle of therapy (mean score for cryotherapy 0.59 vs 1.1 for control group; P<0.05) and all chemotherapeutic courses (mean score for cryotherapy 0.36 vs 0.69 for control group; P< 0.05)	Not reported	Cryotherapy well tolerated by most patients. Two patients reported an “ice cream” headache resulting in cryotherapy refusal
Rocke (1993) [14]	Cryotherapy 60 versus 30 min	89	88	Mean physician-judged mucositis grades 0.58 and 0.79 for 30 vs 60 minutes of cryotherapy (P=0.37). Mean patient-graded mucositis scores were 0.73 and 1.00 (P=0.09)	Not reported	Few subjects discontinued cryotherapy prematurely because of nausea, headache, or chill
Mahood (1991) [15]	Cryotherapy versus no cryotherapy	50	45	Mean physician-judged mucositis grade for cryotherapy 0.9 vs 1.9 for control (P=0.0002). Mean patient-graded toxicity 1.1 for cryotherapy vs 2.4 for control (P=0.0001)	Not reported	Cryotherapy well tolerated by most. Few patients noted mild, temporary mouth numbness or “ice cream headache" which rapidly resolved after cessation of cryotherapy. Some ascribed nausea to cryotherapy
Kakoei (2013) [16]	Cryotherapy versus no cryotherapy	NR	NR	Mean pain intensity in the control group significantly increased with time (P<0.001), whereas cryotherapy group showed no significant change with time (P>0.05)	Patients’ self-assessment in control group significantly higher oral discomfort with time (P=0.012) vs cryotherapy group with no significant changes during study (P>0.05)	Not reported

Abbreviation: SE – standard error; auto- autologous; allo – allogeneic; OAG – Oral Assessment Guide; WCCNR - Western Consortium Cancer Nursing Research Scale; OR – odds ratio; CI – confidence interval

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