Interventions for preventing oral mucositis in patients with cancer receiving treatment

Riley, Philip; Glenny, Anne-Marie; Worthington, Helen V.; Littlewood, Anne; Clarkson, Jan E.; McCabe, Martin G.

Published in:
Cochrane Database of Systematic Reviews

DOI:
10.1002/14651858.CD011552.pub2

Publication date:
2015

Document Version
Publisher's PDF, also known as Version of record

Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for preventing oral mucositis in patients with cancer receiving treatment: oral cryotherapy (Review)

Riley P, Glenny AM, Worthington HV, Littlewood A, Clarkson JE, McCabe MG

Riley P, Glenny AM, Worthington HV, Littlewood A, Clarkson JE, McCabe MG.
Interventions for preventing oral mucositis in patients with cancer receiving treatment: oral cryotherapy.
Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD011552.
DOI: 10.1002/14651858.CD011552.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Interventions for preventing oral mucositis in patients with cancer receiving treatment: oral cryotherapy

Philip Riley[1], Anne-Marie Glenny[1], Helen V Worthington[1], Anne Littlewood[1], Jan E Clarkson[2], Martin G McCabe[3]

[1]Cochrane Oral Health Group, School of Dentistry, The University of Manchester, Manchester, UK. [2]Division of Oral Health Sciences, University of Dundee, Dundee, UK. [3]Centre for Paediatric, Teenage and Young Adult Cancer, The University of Manchester, Manchester, UK

Contact address: Philip Riley, Cochrane Oral Health Group, School of Dentistry, The University of Manchester, JR Moore Building, Oxford Road, Manchester, M13 9PL, UK. philip.riley@manchester.ac.uk.

Editorial group: Cochrane Oral Health Group
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2016.

Citation: Riley P, Glenny AM, Worthington HV, Littlewood A, Clarkson JE, McCabe MG. Interventions for preventing oral mucositis in patients with cancer receiving treatment: oral cryotherapy. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.: CD011552. DOI: 10.1002/14651858.CD011552.pub2.

ABSTRACT

Background

Oral mucositis is a side effect of chemotherapy, head and neck radiotherapy, and targeted therapy, affecting over 75% of high risk patients. Ulceration can lead to severe pain and difficulty eating and drinking, which may necessitate opioid analgesics, hospitalisation and nasogastric or intravenous nutrition. These complications may lead to interruptions or alterations to cancer therapy, which may reduce survival. There is also a risk of death from sepsis if pathogens enter the ulcers of immunocompromised patients. Ulcerative oral mucositis can be costly to healthcare systems, yet there are few preventive interventions proven to be beneficial. Oral cryotherapy is a low-cost, simple intervention which is unlikely to cause side-effects. It has shown promise in clinical trials and warrants an up-to-date Cochrane review to assess and summarise the international evidence.

Objectives

To assess the effects of oral cryotherapy for preventing oral mucositis in patients with cancer who are receiving treatment.

Search methods

We searched the following databases: the Cochrane Oral Health Group Trials Register (to 17 June 2015), the Cochrane Central Register of Controlled Trials (CENTRAL) (*Cochrane Library* 2015, Issue 5), MEDLINE via Ovid (1946 to 17 June 2015), EMBASE via Ovid (1980 to 17 June 2015), CANCERLIT via PubMed (1950 to 17 June 2015) and CINAHL via EBSCO (1937 to 17 June 2015). We searched the US National Institutes of Health Trials Registry, and the WHO Clinical Trials Registry Platform for ongoing trials. No restrictions were placed on the language or date of publication when searching databases.

Selection criteria

We included parallel-design randomised controlled trials (RCTs) assessing the effects of oral cryotherapy in patients with cancer receiving treatment. We used outcomes from a published core outcome set registered on the COMET website.

Data collection and analysis

Two review authors independently screened the results of electronic searches, extracted data and assessed risk of bias. We contacted study authors for information where feasible. For dichotomous outcomes, we reported risk ratios (RR) and 95% confidence intervals (CI). For continuous outcomes, we reported mean differences (MD) and 95% CIs. We pooled similar studies in random-effects meta-analyses. We reported adverse effects in a narrative format.

Main results

We included 14 RCTs analysing 1280 participants. The vast majority of participants did not receive radiotherapy to the head and neck, so this review primarily assesses prevention of chemotherapy-induced oral mucositis. All studies were at high risk of bias. The following results are for the main comparison: oral cryotherapy versus control (standard care or no treatment).

Adults receiving fluorouracil-based (5FU) chemotherapy for solid cancers

Oral cryotherapy probably reduces oral mucositis of any severity (RR 0.61, 95% CI 0.52 to 0.72, 5 studies, 444 analysed, moderate quality evidence). In a population where 728 per 1000 would develop oral mucositis, oral cryotherapy would reduce this to 444 (95% CI 379 to 524). The number needed to treat to benefit one additional person (NNTB), i.e. to prevent them from developing oral mucositis, is 4 people (95% CI 3 to 5).

The results were similar for moderate to severe oral mucositis (RR 0.52, 95% CI 0.41 to 0.65, 5 studies, 444 analysed, moderate quality evidence). NNTB 4 (95% CI 4 to 6).

Severe oral mucositis is probably reduced (RR 0.40, 95% CI 0.27 to 0.61, 5 studies, 444 analysed, moderate quality evidence). Where 300 per 1000 would develop severe oral mucositis, oral cryotherapy would reduce this to 120 (95% CI 81 to 183), NNTB 6 (95% CI 5 to 9).

Adults receiving high-dose melphalan-based chemotherapy before haematopoietic stem cell transplantation (HSCT)

Oral cryotherapy may reduce oral mucositis of any severity (RR 0.59, 95% CI 0.35 to 1.01, 5 studies, 270 analysed, low quality evidence). Where 824 per 1000 would develop oral mucositis, oral cryotherapy would reduce this to 486 (95% CI reduced to 289 to increased to 833). The NNTB is 3, although the uncertainty surrounding the effect estimate means that the 95% CI ranges from 2 NNTB, to 111 NNTH (number needed to treat in order to harm one additional person, i.e. for one additional person to develop oral mucositis).

The results were similar for moderate to severe oral mucositis (RR 0.43, 95% CI 0.17 to 1.09, 5 studies, 270 analysed, low quality evidence). NNTB 3 (95% CI 2 NNTB to 17 NNTH).

Severe oral mucositis is probably reduced (RR 0.38, 95% CI 0.20 to 0.72, 5 studies, 270 analysed, moderate quality evidence). Where 427 per 1000 would develop severe oral mucositis, oral cryotherapy would reduce this to 162 (95% CI 85 to 308), NNTB 4 (95% CI 3 to 9).

Oral cryotherapy was shown to be safe, with very low rates of minor adverse effects, such as headaches, chills, numbness/taste disturbance, and tooth pain. This appears to contribute to the high rates of compliance seen in the included studies.

There was limited or no evidence on the secondary outcomes of this review, or on patients undergoing other chemotherapies, radiotherapy, targeted therapy, or on comparisons of oral cryotherapy with other interventions or different oral cryotherapy regimens. Therefore no further robust conclusions can be made. There was also no evidence on the effects of oral cryotherapy in children undergoing cancer treatment.

Authors' conclusions

We are confident that oral cryotherapy leads to large reductions in oral mucositis of all severities in adults receiving 5FU for solid cancers. We are less confident in the ability of oral cryotherapy to reduce oral mucositis in adults receiving high-dose melphalan before HSCT. Evidence suggests that it does reduce oral mucositis in these adults, but we are less certain about the size of the reduction, which could be large or small. However, we are confident that there is an appreciable reduction in severe oral mucositis in these adults.

This Cochrane review includes some very recent and currently unpublished data, and strengthens international guideline statements for adults receiving the above cancer treatments.

PLAIN LANGUAGE SUMMARY

Can keeping the mouth cold during cancer treatment help to prevent mouth soreness and ulcers in children and adults?

Review question

This review has been produced to assess whether or not keeping the mouth cold during cancer treatment, by using ice, ice-cold water, ice cream or ice lollies/popsicles, can help prevent mouth soreness and ulcers in children and adults.

Background

People receiving treatment for cancer are at risk of developing a sore mouth and ulcers as a side effect. This side effect is called oral mucositis and affects over 75% of high-risk patients (those receiving radiotherapy to the head and neck or high-dose chemotherapy). The pain caused by this condition can be severe and can stop the person's ability to eat and drink, which may mean they need to take strong pain killers, stay in hospital and be fed through a tube into their stomach, or even into their veins. This in turn can lead to disruption to their cancer treatment, meaning they are not receiving the best possible treatment. The results may be a reduction in the patient's chances of

survival, and increased costs to the healthcare system. Cancer patients have weakened immune systems due to their treatment, meaning that their bodies are less able to fight infections. This can be a problem if bacteria enter the body through the ulcer, which is an open wound. This can lead to sepsis (a dangerous inflammatory reaction of the body to infection), which requires antibiotics and hospitalisation, and can cause death.

Oral cryotherapy is the cooling of the mouth using ice, ice-cold water, ice cream or ice lollies/popsicles. It is thought to help prevent oral mucositis in people receiving certain types of chemotherapy because the coldness makes the blood vessels in the mouth more narrow, and this reduces the amount of blood containing chemotherapy drugs from reaching the mouth and causing oral mucositis. It is a low-cost, natural treatment without serious side effects.

Study characteristics

Authors from the Cochrane Oral Health Group carried out this review of existing studies and the evidence is current up to 17 June 2015. It includes 14 studies published from 1991 to 2015 in which 1316 participants were randomised (1280 of whom were included in the analyses) to receive oral cryotherapy versus standard care (usually saline mouthrinses) or no treatment or a different treatment or a different method of oral cryotherapy, and the number of people developing oral mucositis of different severities was compared. Nearly all the evidence was on adults receiving oral cryotherapy versus standard care or no treatment. This evidence fell into two main groups: 1) adults receiving fluorouracil-based (5FU) treatment for solid cancers; or 2) adults receiving high-dose melphalan-based cancer treatment before haematopoietic stem cell transplantation (HSCT). HSCT is given to help the body to produce all types of blood cells, which are destroyed during cancer treatment.

Key results

There is evidence showing that oral cryotherapy can lead to large reductions in the numbers of adults who get oral mucositis of all severities after receiving 5FU-based treatment for solid cancers. There is less certain evidence to suggest that oral cryotherapy may reduce the numbers of adults who get oral mucositis after receiving high-dose melphalan-based cancer treatment prior to HSCT. The evidence suggests that it does reduce oral mucositis in these adults, but the size of the reduction is much less certain. However, there is more certain evidence that there is a large reduction in severe oral mucositis in these adults.

Oral cryotherapy did not cause any serious side effects in any of the participants of these studies, and most people seemed able to carry it out properly and complete it.

Quality of the evidence

The evidence presented, on the main outcome of whether or not people developed oral mucositis of all severities, is of moderate (because the nature of the oral cryotherapy treatment meant that the studies could not be 'blinded' which is a desirable characteristic of these studies) to low quality (because in addition to the above problem, the results of the individual studies were too different to give a precise result when they were combined).

Summary of findings for the main comparison. Cryotherapy versus control for preventing oral mucositis in adults receiving fluorouracil-based treatment for solid cancers

Cryotherapy versus control for preventing oral mucositis in adults receiving fluorouracil-based treatment for solid cancers

Patient or population: adults** with solid cancers receiving fluorouracil-based cancer treatment
Setting: hospital
Intervention: cryotherapy
Comparison: control (no treatment or routine care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with cryotherapy				
Oral mucositis (any)	728 per 1000	444 per 1000 (379 to 524)	RR 0.61 (0.52 to 0.72)	444 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Oral cryotherapy reduced the risk of developing oral mucositis by 39% (95% CI 28% to 48%). We would need to treat 4 people (95% CI 3 to 5 people) with oral cryotherapy to prevent 1 additional person from developing oral mucositis
Oral mucositis (moderate + severe)	530 per 1000	276 per 1000 (217 to 344)	RR 0.52 (0.41 to 0.65)	444 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Oral cryotherapy reduced the risk of developing moderate to severe oral mucositis by 48% (95% CI 35% to 59%). We would need to treat 4 people (95% CI 4 to 6 people) with oral cryotherapy to prevent 1 additional person from developing moderate to severe oral mucositis
Oral mucositis (severe)	300 per 1000	120 per 1000 (81 to 183)	RR 0.40 (0.27 to 0.61)	444 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Oral cryotherapy reduced the risk of severe oral mucositis by 60% (95% CI 39% to 73%). We would need to treat 6 people (95% CI 5 to 9 people) with oral cryotherapy to prevent 1 additional person from developing severe oral mucositis
Interruptions to cancer treatment	400 per 1000	176 per 1000 (80 to 380)	RR 0.44 (0.20 to 0.95)	80 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2 3 4]	Oral cryotherapy reduced the risk of treatment interruption by 56% (95% CI 5% to 80%). We would need to treat 5 people (95% CI 4 to 50 people) with oral cryotherapy to prevent 1 additional person from having a treatment interruption

Oral pain (1 to 5 scale: 1 = never, 2 = 1 day of week, 3 = 2 to 3 days of week, 4 = most of week, 5 = 7 days of week)	The mean oral pain (1 to 5 scale) was 3.64	The mean oral pain (1 to 5 scale) in the cryotherapy group was 1.93 lower (2.37 to 1.49 lower)	-	80 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2 3 4]	The duration of oral pain experienced was less in the oral cryotherapy group (Additional Table 1)
Quality of life	No studies assessed this outcome					
Normalcy of diet (days of total parenteral nutrition)	No studies assessed this outcome					
Duration of hospitalisation (days)	No studies assessed this outcome					

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __RCT:__ randomised controlled trial; __RR:__ risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] All 5 studies at high risk of performance and detection bias
[2] Single study at high risk of performance and detection bias
[3] Low sample size and wide confidence interval
[4] Indirect due to single study in 1 setting (in terms of country, healthcare system, and participants potentially differing from other countries)
** There were no studies conducted on children

Summary of findings 2. Cryotherapy versus control for preventing oral mucositis in adults receiving high-dose melphalan-based treatment prior to haematopoietic stem cell transplantation for haematological cancers

Cryotherapy versus control for preventing oral mucositis in adults receiving high-dose melphalan-based treatment prior to haematopoietic stem cell transplantation for haematological cancers

Patient or population: adults** with haematological cancers receiving high-dose melphalan-based treatment prior to haematopoietic stem cell transplantation
Setting: hospital
Intervention: cryotherapy

Comparison: control (no treatment or routine care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with cryotherapy				
Oral mucositis (any)	824 per 1000	486 per 1000 (289 to 833)	RR 0.59 (0.35 to 1.01)	270 (5 RCTs)	⊕⊕⊖⊖ LOW [1,2]	Oral cryotherapy appears to reduce the risk of developing oral mucositis. However, there is great uncertainty about our estimate, and there is an extremely small chance of a 1% increase in the risk of developing oral mucositis compared to control. The point estimate suggests a 41% reduction in the risk of developing oral mucositis, with the confidence interval ranging from a 65% reduction to a 1% increase in risk. We would need to treat 3 people with oral cryotherapy to prevent 1 additional person from developing oral mucositis, with the confidence interval ranging from 2 people (to prevent 1 additional oral mucositis case) to 111 people to cause 1 additional person to develop oral mucositis
Oral mucositis (moderate + severe)	679 per 1000	292 per 1000 (115 to 741)	RR 0.43 (0.17 to 1.09)	270 (5 RCTs)	⊕⊕⊖⊖ LOW [1,2]	Oral cryotherapy appears to reduce the risk of developing moderate to severe oral mucositis. However, there is great uncertainty about our estimate, and there is a very small chance of a 9% increase in the risk of developing moderate to severe oral mucositis compared to control. The point estimate suggests a 57% reduction in the risk of developing moderate to severe oral mucositis, with the confidence interval ranging from an 83% reduction to a 9% increase in risk. We would need to treat 3 people with oral cryotherapy to prevent 1 additional person from developing moderate to severe oral mucositis, with the confidence interval ranging from 2 people (to prevent 1 additional moderate to severe oral mucositis case) to 17 people to cause 1 additional person to develop moderate to severe oral mucositis
Oral mucositis (severe)	427 per 1000	162 per 1000 (85 to 308)	RR 0.38 (0.20 to 0.72)	270 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Oral cryotherapy reduced the risk of developing severe oral mucositis by 62% (95% CI 28% to 80%). We would need to treat 4 people (95% CI 3 to 9 people) with oral cryotherapy to prevent 1 additional person from developing severe oral mucositis
Interruptions to cancer treatment	No studies assessed this outcome					

Oral pain on a 0 (no pain) to 10 (maximum pain) scale	The weighted mean oral pain (0 to 10 scale) was 2.13	The mean oral pain (0 to 10 scale) in the cryotherapy group was 1.5 lower (2.11 to 0.89 lower)	-	85 (2 RCTs)	⊕⊕⊖⊖ LOW [3 4]	Oral cryotherapy reduced oral pain by 70% although the clinical importance of a 1.5 point-reduction on a 0 to 10 scale is questionable
Quality of life	1 study assessed this outcome but the data are currently unavailable as the study report and analysis have not yet been completed					
Normalcy of diet (days of total parenteral nutrition - TPN)	The mean number of days of TPN was 7	The mean number of days of TPN in the intervention group was 2.18 days fewer (4.33 to 0.03 fewer)	-	78 (1 RCT)	⊕⊖⊖⊖ VERY LOW [5 6 7]	Oral cryotherapy reduced the duration of TPN by 2.18 days. There was some additional very low quality evidence, from a single small study at high risk of bias, reporting only median, range and P value, that oral cryotherapy reduced the number of days of TPN (Additional Table 1)
Duration of hospitalisation (days)	The mean duration of hospitalisation (days) was 0	The mean duration of hospitalisation (days) in the intervention group was 1.39 undefined fewer (2.97 fewer to 0.19 more)	-	123 (2 RCTs)	⊕⊕⊖⊖ LOW [3 4]	There is insufficient evidence to show that oral cryotherapy reduces the duration of hospitalisation. This is supported by additional very low quality evidence, from a single small study at high risk of bias, reporting only median, range and P value, that there is insufficient evidence to show a reduction in this outcome (Additional Table 1)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio; **TPN:** total parenteral nutrition

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] All 5 studies at risk of performance and detection bias, with 1 study at added risk of attrition bias
[2] The I^2 value indicates that a considerable amount (> 90%) of the variability in effect estimates is due to heterogeneity rather than chance
[3] Both studies at high risk of performance and detection bias
[4] Low sample size from 2 small studies
[5] Single study at high risk of performance and detection bias
[6] Low sample size and wide confidence interval

[7] Indirect due to single study in 1 setting (in terms of country, healthcare system, and participants potentially differing from other countries)
** There were no studies conducted on children

BACKGROUND

Description of the condition

Treating cancer with chemotherapy, radiotherapy of the head and neck, or targeted therapy can cause toxic oral side effects (Al-Dasooqi 2013; Scully 2006; Sonis 2004). Perhaps the most widely researched of these side effects is oral mucositis (Al-Dasooqi 2013), which affects at least 75% of high risk patients (those receiving head and neck radiotherapy or high-dose chemotherapy) (Scully 2006). Oral mucositis may be under-reported in lower risk groups for various reasons: their tendency to be outpatients with less observation; less reporting of moderate mucositis; or patients and clinicians wishing to avoid any disruption to optimal cancer treatment (Scully 2006).

Simply put, oral mucositis affects the oral mucosa (the mucous membrane of moist tissue lining the oral cavity) and can lead to the development of lesions (ulcers). However, the process that leads to oral mucositis is complex and multifactorial, with Sonis' five phase model being the currently accepted explanation for the sequence of events underlying the condition (Sonis 2004; Sonis 2009).

1. Initiation: DNA damage caused by chemotherapy or radiotherapy results in the loss of ability to proliferate in the basal cells of the epithelium (the external layers of cells lining the oral mucosa). This produces reactive oxygen species (ROS).
2. Primary damage response: Radiotherapy, chemotherapy, ROS, and DNA strand breaks all contribute to the activation of transcription factors such as nuclear factor kappa beta (NF-Kβ), and sphingomyelinases. All this leads to the upregulation of pro-inflammatory cytokines (e.g. tumour necrosis factor alpha - TNF-α), nitric oxide, ceramide, and matrix metalloproteinases, resulting in the thinning of the epithelium through tissue injury and cell death, culminating with the destruction of the oral mucosa.
3. Signal amplification: Some of the molecules in the previous phase can lead to the exacerbation and prolonging of tissue injury through positive or negative feedback (e.g. TNF-α can positively feedback on NF-Kβ thus inducing more pro-inflammatory cytokine production).
4. Ulceration: Bacteria colonise ulcers and their cell wall products infiltrate the submucosa (the connective tissues beneath the oral mucosa), activating tissue macrophages (white blood cells that respond to infection or damaged/dead cells), which results in further production of pro-inflammatory cytokines, inflammation, and pain.
5. Healing: Signalling from the extracellular matrix of the submucosa results in epithelial proliferation and differentiation, and thus a thickening of the epithelium. The local oral flora are reinstated.

Understanding of the pathobiology leading to mucosal toxicity as a result of targeted therapies (e.g. mammalian target of rapamycin (mTOR) inhibitor-associated stomatitis - mIAS) is currently limited, but it is thought to differ from chemotherapy- and radiotherapy-induced mucositis, and the clinical presentation of the ulcers is more similar to aphthous stomatitis (Al-Dasooqi 2013; Boers-Doets 2013; Peterson 2015).

Chemotherapy-induced oral mucositis is regarded as an acute condition, with ulceration normally occurring one week after treatment, and resolving within three weeks of treatment (Sonis 2009). Radiotherapy-induced oral mucositis is chronic in nature, with ulceration normally occurring around two weeks into a seven-week treatment cycle, and resolving three to four weeks after treatment has ended (Sonis 2009).

Ulceration is the most significant phase as it leads to pain of varying severity, and difficulties with eating, swallowing, and talking (Scully 2006). This in turn leads to the consumption of pain relief medication, requirement for nutritional support (e.g. a feeding tube), treatment of the oral mucositis, specialist oral hygiene care, increased medical appointments and use of staff and resources, and, in some instances, hospitalisation (Jensen 2014; Miller 2001; Trotti 2003). Thus the negative impact on the quality of life of cancer patients, when they are already suffering, is severe (Elting 2008; Epstein 1999). Further problems can occur in immunosuppressed patients if whole bacteria on the ulcer surface cross into the underlying submucosa, potentially leading to bacteraemia and sepsis, which require antibiotics and hospitalisation, and can cause death (Jensen 2014; Peterson 2015; Scully 2006).

Therefore, oral mucositis can be a dose-limiting condition, disrupting a patient's optimal cancer treatment plan and consequentially decreasing their chances of survival (Jensen 2014; Peterson 2015; Sonis 2004). The additional costs associated with oral mucositis can be significant, with one study reporting a median incremental cost of USD 18,515 per patient (Nonzee 2008). These costs have been reported to be as much as USD 42,749 more per patient when ulcerative oral mucositis is present (Sonis 2001).

Description of the intervention

Fluorouracil (5FU) is a common chemotherapy treatment for solid cancers and, in this setting, oral cryotherapy typically involves placing ice chips in the mouth five minutes prior to chemotherapy and continuing for 30 minutes (Lalla 2008). In other settings, such as patients with haematological cancers receiving high-dose melphalan prior to stem cell transplantation, oral cryotherapy is administered for longer periods of time, even as long as seven hours (Lilleby 2006). The ice chips are typically rounded to avoid any sharp edges or corners that may cause irritation to the patient, and also so that they can be easily moved around in the mouth (Karagözoğlu 2005).

The advantages of using cryotherapy over other interventions are its availability, cost-effectiveness, ease of administration, and safety (in terms of lack of side-effects), and that it is well tolerated by patients (Peterson 2013).

How the intervention might work

The use of ice chips in the mouth cools the oral tissues and causes the blood vessels to narrow (vasoconstriction), thus reducing blood flow to the area and therefore also restricting the amounts of the chemotherapy drugs delivered to the tissues (Lalla 2008; Peterson 2013; Scully 2006). Cryotherapy may only be effective in the prevention of oral mucositis in patients receiving chemotherapy drugs that have a short half-life, such as bolus 5-FU, bolus edatrexate, and high-dose melphalan (Lalla 2008; Peterson 2013; Scully 2006). Considering the mechanism by which cryotherapy can prevent oral mucositis caused by chemotherapy, it is unclear whether or not it could have any effect on oral mucositis caused by radiotherapy (Lalla 2008). It is also unclear whether or not

cryotherapy could have any role in the prevention of targeted therapy-induced stomatitis.

Why it is important to do this review

This review is the first of a series that will replace the previously published Cochrane review covering all interventions for the prevention of oral mucositis in patients with cancer receiving treatment (Worthington 2011). The Mucositis Study Group (MSG) of the Multinational Association of Supportive Care in Cancer/ International Society of Oral Oncology (MASCC/ISOO) is a group that was set up in 1998 for the purpose of producing international evidence-based clinical practice guidelines for managing mucositis (both oral and gastrointestinal), which they first published in 2004, with the latest update published in 2014 (Lalla 2014). In order to facilitate the future updating of Cochrane reviews on this topic, and also to make them more usable to clinicians, guideline developers, and consumers, we have decided to divide the original Cochrane review into the same intervention categories as those used by MASCC/ISOO, which are as follows:

- basic oral care/good clinical practice;
- growth factors and cytokines;
- anti-inflammatory agents;
- antimicrobials, mucosal coating agents, anaesthetics, and analgesics;
- laser and other light therapy;
- cryotherapy;
- natural and miscellaneous agents;
- amifostine.

We believe that running in tandem with the MASCC/ISOO categories will enable the Cochrane reviews to more easily feed into such guidelines. We will also be able to be more thorough and rigorous in our assessment and summarising of the evidence in each of the categories, which was not feasible in a single Cochrane review approaching 150 included studies.

It is also important to do this review as it is consistently shown to be the most used review produced by the Cochrane Oral Health Group (in terms of full-text downloads). It was also ranked by an expert panel of oral medicine specialists as being the most important topic in the field of oral medicine in an international prioritisation exercise carried out by the Cochrane Oral Health Group in 2014 (Worthington 2015).

OBJECTIVES

To assess the effects of oral cryotherapy for preventing oral mucositis in patients with cancer who are receiving treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) of parallel design. It is possible to conduct cross-over studies in this area as patients may receive several treatment sessions, with any mucositis completely healing in the periods between the sessions. However, we did not include cross-over data as we cannot discount any period effects, with mucositis risk increasing as patients receive further cycles of treatment (Scully 2006; Sonis 2009). Instead, we used the first-period data only and treated such studies as parallel studies.

Types of participants

We included all patients with cancer who are receiving treatment.

Types of interventions

We included studies comparing oral cryotherapy for the prevention of oral mucositis against usual care, no treatment, or any other treatment to prevent oral mucositis. We also included studies comparing different regimens of oral cryotherapy against each other (head-to-head studies). We planned to include studies of oral mucositis caused by chemotherapy, radiotherapy, and targeted therapy.

We excluded studies with 'complex' interventions for the prevention of mucositis, such as lasers plus cryotherapy versus lasers. We excluded studies assessing different cancer treatments where the primary outcome is survival/cure, with mucositis as a toxicity.

Types of outcome measures

We are in agreement with Williamson 2012 that, if clinical trials and systematic reviews are to be utilised, the outcomes assessed should be those considered important to patients, healthcare professionals, and other key stakeholders. If outcomes and outcome measures are inconsistent across studies, it will not be possible to compare and summarise research, and there is potential for outcome reporting bias, with the selective reporting of results based on statistical significance and favourability (Clarke 2007; Dwan 2008; Williamson 2005). This can lead to exaggerated estimates of effect in systematic reviews of interventions, leading to an incorrect belief that an intervention is more beneficial that it truly is (Clarke 2007). It is thought that the way to address this problem is to develop disease- or condition-specific core outcome sets to be used as a minimum when conducting and reporting clinical trials (Clarke 2007; Williamson 2012).

Therefore we used the core outcome set produced by Bellm 2002, which is registered on the COMET (Core Outcome Measures in Effectiveness Trials) Initiative's website (www.comet-initiative.org), and is the only core outcome set for oral mucositis known to us.

Primary outcomes

Mucositis incidence of any severity. We used mucositis measured on a 0 to 4 point scale (none to severe) and dichotomised it as any mucositis (0 versus 1+), moderate to severe mucositis (0 to 1 versus 2+), and severe mucositis (0 to 2 versus 3+).

Some studies measure mucositis using a composite scale. If it was possible to extract the 'mucositis only' data from the total score, we would have included the data in the analyses. If it was not possible, we would have recorded the composite data in an additional table.

Secondary outcomes

- Interruptions to cancer treatment.
- Oral pain.
- Quality of life.

- Normalcy of diet (including use of percutaneous endoscopic gastrostomy (PEG) feeding tubes or total parenteral nutrition (TPN)).
- Adverse events.
- Number of days in hospital.
- Number of days of treatment with opioid analgesics.
- Number of days unable to take medicine orally.

Search methods for identification of studies

For the identification of studies included or considered for this review, we developed detailed search strategies for each database searched. These were based on the search strategy we developed for MEDLINE (Ovid) (Appendix 3), which we revised appropriately for each database. The study design filter used by the Cochrane Oral Health Group was added to the search of the EMBASE database to limit the search to randomised controlled trials (Appendix 4).

Electronic searches

We searched the following electronic databases:

- the Cochrane Oral Health Group Trials Register (to 17 June 2015) (Appendix 1);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (*Cochrane Library* 2015, Issue 5) (Appendix 2);
- MEDLINE via Ovid (1946 to 17 June 2015) (Appendix 3);
- EMBASE via Ovid (1980 to 17 June 2015) (Appendix 4);
- CANCERLIT via PubMed (1950 to 17 June 2015) (Appendix 5);
- CINAHL via EBSCO (1937 to 17 June 2015) (Appendix 6).

No restrictions were placed on the language or date of publication when searching the electronic databases.

Searching other resources

We searched the following databases for ongoing trials (Appendix 7):

- US National Institutes of Health Trials Registry (http://clinicaltrials.gov) (to 17 June 2015);
- World Health Organization (WHO) International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/default.aspx) (to 17 June 2015).

We only included handsearching done as part of the Cochrane Worldwide Handsearching Programme and uploaded to CENTRAL.

Data collection and analysis

Selection of studies

Two review authors independently screened the titles and abstracts retrieved from the electronic searches. We obtained full-text copies of all studies that appeared to meet the inclusion criteria of the review, or where there was insufficient information in the title or abstract to make a clear judgement. Two review authors independently assessed the full text copies for eligibility and attempted to resolve any disagreements through discussion. We consulted a third review author if we could not resolve disagreements.

On assessing the full text article, we discarded any studies that clearly did not meet the inclusion criteria. We recorded all other studies that did not meet the inclusion criteria, along with reasons for exclusion, in the Characteristics of excluded studies table.

Data extraction and management

Two review authors independently extracted the data from each included study using a specially designed data extraction form, which we first piloted on a small sample of studies. We contacted study authors for clarification or missing data where necessary and feasible. We resolved any disagreements through discussion, consulting a third review author to achieve consensus when necessary.

We recorded the following data for each included study in the Characteristics of included studies table.

- Trial design, location, number of centres, recruitment period.
- Inclusion/exclusion criteria, age and gender of participants, number randomised/analysed, any other potentially important prognostic factors (e.g. cancer type, cancer treatment, etc.).
- Detailed description of the intervention and comparator, including timing and duration. Information on compliance with the cryotherapy regimen.
- Details of the outcomes reported, including method of assessment and time(s) assessed.
- Details of sample size calculations, adverse effects, funding sources, declarations/conflicts of interest.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias of each included study using the Cochrane domain-based, two-part tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We contacted study authors for clarification or missing information where necessary and feasible. We resolved any disagreements through discussion, consulting a third review author to achieve consensus when necessary.

We completed a 'Risk of bias' table for each included study. For each domain of risk of bias, we first described what was reported to have happened in the study. This provided the rationale for our judgement of whether that domain was at low, high, or unclear risk of bias.

We assessed the following domains:

1. sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias);
6. selective outcome reporting (reporting bias);
7. other bias.

We categorised the overall risk of bias of individual studies. Studies were categorised as being at low, high, or unclear risk of bias according to the following criteria:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were at low risk of bias;

- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were at high risk of bias; or
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains were at unclear risk of bias.

We also presented the 'Risk of bias' summary graphically (Figure 1).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

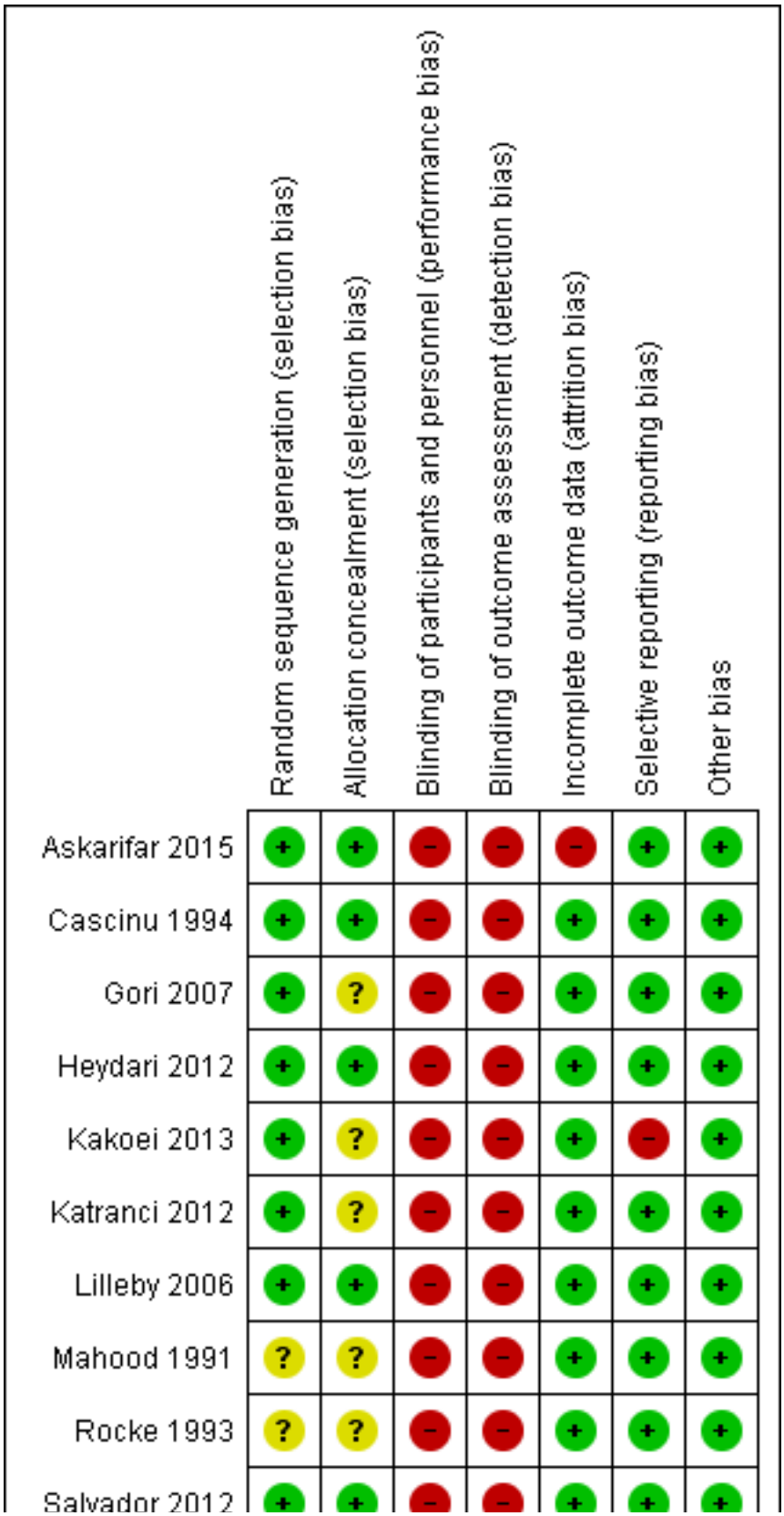
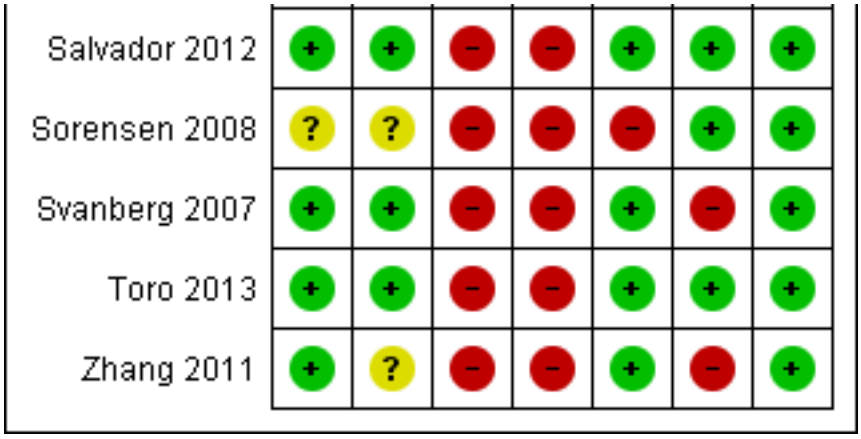


Figure 1. (Continued)



Measures of treatment effect

For continuous outcomes (e.g. oral pain on a visual analogue scale) where studies used the same scale, we used the mean values and standard deviations (SDs) reported in the studies in order to express the estimate of effect as mean difference (MD) with 95% confidence interval (CI). Where different scales were used, we would have considered expressing the treatment effect as standardised mean difference (SMD) with 95% CI.

For dichotomous outcomes (e.g. mucositis of any severity/no mucositis), we expressed the estimate of effect as a risk ratio (RR) with 95% CI.

Unit of analysis issues

The participant was the unit of analysis.

Dealing with missing data

We attempted to contact the author(s) of all included studies, where feasible, for clarification, missing data, and details of any other outcomes that may have been measured but not reported. We used the methods described in Section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* to estimate missing SDs (Higgins 2011). We did not use any other statistical methods or perform any further imputation to account for missing data.

Assessment of heterogeneity

When a sufficient number of studies were included in any meta-analyses, we assessed clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions, and the outcomes. We also assessed heterogeneity statistically using a Chi^2 test, where a P value < 0.1 indicates statistically significant heterogeneity. We quantified heterogeneity using the I^2 statistic. A guide to interpretation of the I^2 statistic given in Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* is as follows (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If at least 10 studies were included in a meta-analysis, we planned to assess publication bias according to the recommendations on testing for funnel plot asymmetry (Egger 1997), as described in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If asymmetry was identified, we would examine possible causes. We were not able to assess publication bias in this way because, although we had a sufficient number of studies in our meta-analyses for the primary outcome, they were split into subgroups containing less than 10 studies, with no pooling of the subgroup totals.

Data synthesis

We only carried out meta-analyses where there were studies of similar comparisons reporting the same outcomes. We combined MDs for continuous data, and RRs for dichotomous data. Our general approach was to use a random-effects model. With this approach, the CIs for the average intervention effect were wider than those that would have been obtained using a fixed-effect approach, leading to a more conservative interpretation.

We used an additional table to report the results from studies not suitable for inclusion in a meta-analysis.

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses according to type of cancer treatment. We stated in the protocol that we would also use both type of cancer treatment and cancer type as categories for subgroup analyses. However, these categories are very closely related, so it did not make sense to do so. We also would have considered age group (children versus adults) as a category for subgroup analyses, if there had been sufficient numbers of studies with these differing populations.

Sensitivity analysis

As all studies were at high risk of both performance and detection bias, it was not possible to test the robustness of our results by performing sensitivity analyses based on excluding the studies at unclear or high risk of bias from the analyses.

If any meta-analyses had included several small studies and a single very large study, we would have undertaken a sensitivity analysis comparing the effect estimates from both random-effects

and fixed-effect models. If these were different we would have reported on both analyses as part of the results section, and we would have considered possible interpretation.

Presentation of main results

We produced a 'Summary of findings' table for each comparison that included more than one study, and for the main outcomes (listed below). We produced a separate table for each of the two main cancer treatment types in this review: treatment of solid cancers and treatment of haematological cancers. We used GRADE methods (GRADE 2004), and GRADEpro 2014 software. We assessed the quality of the body of evidence for each comparison and outcome by considering the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates, and the risk of publication bias. We categorised the quality of each body of evidence as high, moderate, low, or very low.

Main outcomes:

- mucositis incidence;
- interruptions to cancer treatment;
- oral pain;
- quality of life;
- normalcy of diet;
- adverse events;
- number of days in hospital.

RESULTS

Description of studies

Results of the search

The electronic searches retrieved 745 references to studies. After removing duplicates, this figure was reduced to 426. We examined the titles and abstracts of these references and discarded all but 40 with no further assessment. Where possible, we obtained full-text copies of these 40 potentially relevant references, and we linked any multiple references to the same study under a single study ID, resulting in a total of 32 studies. We excluded 11 studies (11 references) at this stage. The remaining 21 studies (29 references) appeared to meet our inclusion criteria and we were able to include 14 of these studies (20 references). Of the remaining 7 studies (9 references), 5 studies (7 references) are awaiting assessment due to insufficient information in the abstract or trials registry record to allow inclusion in the review, and 2 studies (2 references) are ongoing. We present this process as a flow chart in Figure 2.

Figure 2. Study flow diagram

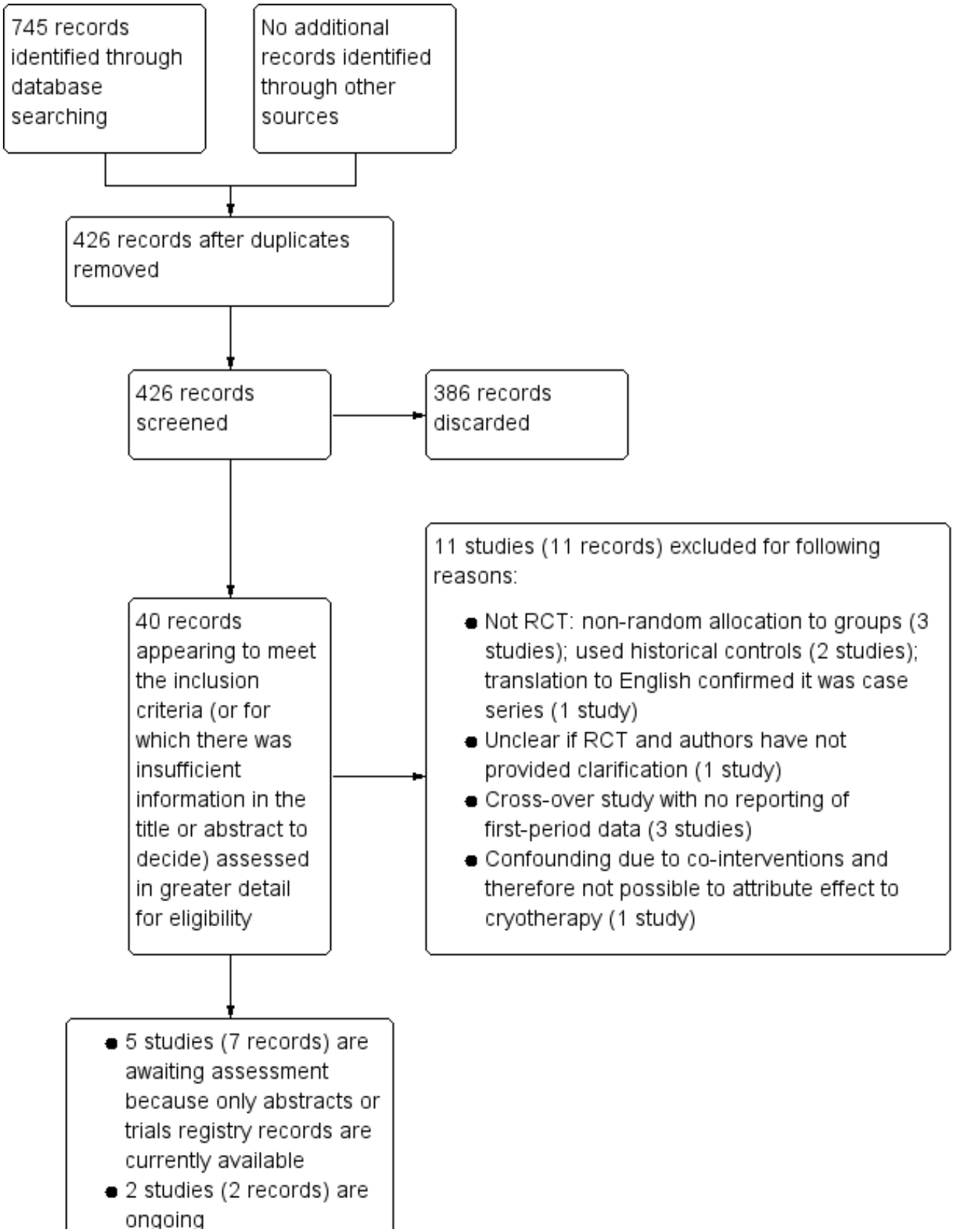
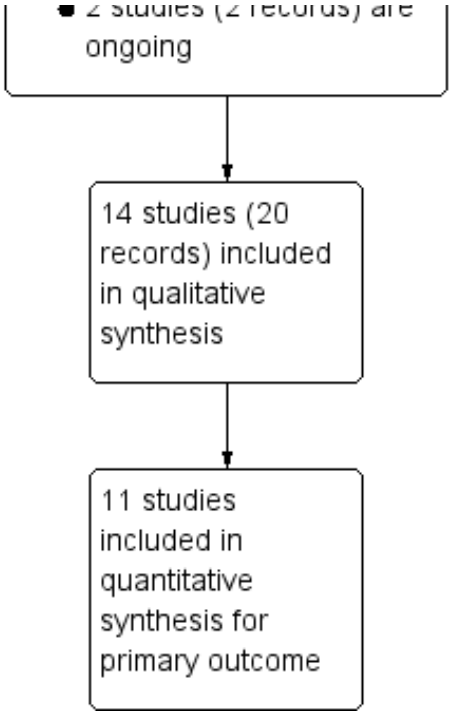


Figure 2. (Continued)



Included studies

Fourteen studies were included in this review (*see* Characteristics of included studies tables).

Characteristics of the trial designs and settings

Twelve studies were of parallel design, with the remaining two studies using a cross-over design (Mahood 1991; Rocke 1993). We treated the cross-over studies as parallel studies by using only the first-period data. Eleven studies had two arms, whilst two studies had three arms (Sorensen 2008; Toro 2013), one of which was excluded from Toro 2013 as we felt that the comparison of the third group, using supersaturated calcium phosphate rinse (Caphosol®), with the co-intervention of cryotherapy plus saline may be confounded. Another study had four arms, with one of those arms being excluded from this review because it involved treating oral mucositis rather than preventing it (Zhang 2011). Four studies were conducted in the USA (Lilleby 2006; Mahood 1991; Rocke 1993; Toro 2013), three in Iran (Askarifar 2015; Heydari 2012; Kakoei 2013), two in Italy (Cascinu 1994; Gori 2007), and one in each of Turkey (Katranci 2012), Canada (Salvador 2012), Denmark (Sorensen 2008), Sweden (Svanberg 2007), and China (Zhang 2011). There were nine single-centre studies, one with two centres (Heydari 2012), and four that were multicentre but were unclear about how many centres were involved (Gori 2007; Mahood 1991; Rocke 1993; Sorensen 2008). Five studies did not report the duration of the trial from start to finish, but the remaining studies ranged in total duration from six months to five years.

Eight studies reported details of a sample size calculation: two of these studies achieved their required sample size (Kakoei 2013; Salvador 2012), two did not (Sorensen 2008; Toro 2013), three were unclear whether or not the sample size requirements were met (Askarifar 2015; Gori 2007; Lilleby 2006), and the remaining study did not use the primary outcome of oral mucositis incidence/severity to calculate the required sample size (Svanberg 2007). Six studies did not mention sample size calculation (Cascinu 1994; Heydari 2012; Katranci 2012; Mahood 1991; Rocke 1993; Zhang 2011).

Eleven studies reported on funding sources, all of which were in the form of independent funding from government, charities or universities. The remaining three studies did not report any funding sources (Cascinu 1994; Katranci 2012; Zhang 2011). Four studies declared that there were no conflicts of interest (Askarifar 2015; Katranci 2012; Salvador 2012; Toro 2013), whilst the other ten studies did not mention conflicts of interest.

Characteristics of the participants

There were 1316 participants randomised to interventions (including only the intervention groups relevant to this review), of which 1280 were included in the studies' analyses. Age ranged from 8 to 85 years across the studies, with mean or median ages ranging between 36 to 63 years. However, only one study reported the inclusion of children, although this was a small minority (Gori 2007). In general, there were more males than females in the studies. Only one study included more females than males, but this was because 50% of the participants had breast cancer (Heydari 2012). One study involved participants undergoing radiotherapy to the head and neck, with the remaining studies involving participants undergoing chemotherapy. No studies involved targeted therapy.

Solid cancers

In eight studies, the participants had solid cancers. In four of these studies, the majority of cancers were gastrointestinal, colorectal, and breast (Cascinu 1994; Heydari 2012; Katranci 2012; Sorensen 2008), whilst two studies did not state the types of cancers involved (Mahood 1991; Rocke 1993), one study included only head and neck cancers (Kakoei 2013), and one study included only bone

cancer (osteosarcoma) (Zhang 2011). The cancer treatment in these studies of solid cancers mostly involved fluorouracil (5FU), normally in conjunction with leucovorin (Cascinu 1994; Heydari 2012; Katranci 2012; Mahood 1991; Rocke 1993; Sorensen 2008). The study on participants with head and neck cancers was the only study included in this review that assessed the effects of oral cryotherapy for preventing oral mucositis in people receiving radiotherapy-only (Kakoei 2013). In the remaining study including participants with osteosarcoma (Zhang 2011), the cancer treatment was high-dose methotrexate plus vincristine and leucovorin.

Haematological cancers

In five studies, the participants had haematological cancers: multiple myeloma (Lilleby 2006; Salvador 2012; Toro 2013), Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma (Askarifar 2015), and mixed (Gori 2007). The cancer treatment in these studies involved high-dose melphalan (Askarifar 2015; Lilleby 2006; Salvador 2012; Toro 2013), or low-dose methotrexate for preventing graft-versus-host disease (GVHD), which is the rejection of donor cells, after allogeneic (cells from a donor) stem cell transplantation (Gori 2007).

One study included one participant in each group (2.6%) with solid cancer (testicular), with the remaining participants all having a mixture of haematological cancers (Svanberg 2007). The cancer treatment in this study was mixed, with the majority (73%) of participants receiving either high-dose melphalan or BEAC regimen (carmustine, etoposide, cytarabine and cyclophosphamide).

In these six studies involving haematological cancers, participants also had haematopoietic stem cell transplantation (HSCT) following chemotherapy. However, in Gori 2007, the authors assessed the effects of oral cryotherapy for preventing oral mucositis due to further chemotherapy given after HSCT for the purpose of preventing GVHD.

Characteristics of the interventions and comparisons

One study compared different durations (30 minutes versus 60 minutes) of oral cryotherapy (Rocke 1993). Eight studies compared oral cryotherapy against no treatment (Cascinu 1994; Gori 2007; Heydari 2012; Kakoei 2013; Mahood 1991; Salvador 2012; Svanberg 2007; Toro 2013). In four of these studies, both the oral cryotherapy group and control group received standard oral care (Kakoei 2013; Salvador 2012; Svanberg 2007; Toro 2013), so the comparison can be thought of as being oral cryotherapy versus no treatment (no extra treatment). One of these four studies also had a supersaturated calcium phosphate rinse (Caphosol®) group which we excluded from this review because we did not consider this intervention versus cryotherapy plus saline rinse to be an eligible comparison, due to potential confounding from the latter co-intervention (Toro 2013). Another four studies compared oral cryotherapy against some form of standard oral care: saline rinse (Askarifar 2015; Lilleby 2006; Sorensen 2008), unspecified (Katranci 2012). One of these studies had a third intervention group that received chlorhexidine rinse (Sorensen 2008). The remaining study had three eligible intervention groups and compared oral cryotherapy against leucovorin rinse and high-dose leucovorin rinse (Zhang 2011).

Most studies used ice chips for cooling the oral cavity, with one study also allowing an alternative option of using popsicles (a flavoured ice lolly) (Gori 2007), and another study allowed the alternative option of ice-cold water (Svanberg 2007). Two studies used ice cubes (Askarifar 2015; Kakoei 2013), possibly suggesting a larger size of ice pieces, whereas another two studies used crushed ice (Sorensen 2008; Toro 2013), possibly suggesting smaller ice pieces. One study exclusively used ice water (Zhang 2011).

The duration of treatment with oral cryotherapy varied widely according to chemotherapy regimen, and was unclear in five studies (Askarifar 2015; Cascinu 1994; Svanberg 2007; Toro 2013; Zhang 2011). The most consistent cryotherapy schedule was in those participants receiving fluorouracil (5FU) and leucovorin, and typically consisted of 30 minutes (45 minutes in Sorensen 2008; 60 minutes in half the participants in Rocke 1993) per day for five consecutive days. The longest duration of oral cryotherapy was seven hours (Lilleby 2006).

Characteristics of the outcomes

We wrote to authors of 11 of the included studies to ask if they had measured any other outcomes than those mentioned in the study reports. We did not write to authors of three of the included studies as they were published before the year 2000 and we thought it was unfeasible to obtain any extra data (Cascinu 1994; Mahood 1991; Rocke 1993). The authors of one study have since provided us with data for two outcomes not reported in their study: 'interruptions to cancer treatment' and 'oral pain' (Heydari 2012).

Primary outcome

For the primary outcome of oral mucositis, we were interested in both the presence/absence of oral mucositis, and also different levels of severity. All 14 included studies measured oral mucositis. Eleven studies used the WHO 0 to 4 scale, or a scale based on this. Three studies used the National Cancer Institute common toxicity criteria (NCI-CTC) 0 to 4 scale (Lilleby 2006; Sorensen 2008; Zhang 2011). The WHO and NCI-CTC scales include both subjective and objective elements, and are highly comparable (Appendix 8), such that it is not necessary to use standardised mean difference when including both types of measurement in a meta-analysis. One study used a modified version of the Oral Mucositis Assessment Scale (OMAS) as the primary tool for measurement of oral mucositis, but provided us with full data according to the WHO scale (Svanberg 2007). The OMAS is an objective scale, measuring ulceration (0 to 3 scale) and erythema (0 to 2 scale) at nine different sites in the oral cavity (Appendix 8).

Eight studies reported the data in our preferred format which was the maximum oral mucositis score, on a 0 to 4 scale, experienced by each participant over the length of the study (Cascinu 1994; Gori 2007; Heydari 2012; Lilleby 2006; Mahood 1991; Rocke 1993; Sorensen 2008; Toro 2013). One study reported the incidence of any oral mucositis (i.e. grades 1 to 4), but appeared to selectively report the incidence of each grade on a single day quite early in the study (i.e. not the maximum score experienced by each participant over the length of the study) (Zhang 2011). Four studies reported the mean oral mucositis score on multiple assessment days (Askarifar 2015; Kakoei 2013; Salvador 2012; Svanberg 2007), whilst the remaining study reported the incidence of each oral mucositis grade on multiple assessment days (Katranci 2012).

We wrote to all authors who reported means or on multiple assessment days or both, to request incidence data in the form of a single table reporting the maximum oral mucositis score (on a 0 to 4 scale) experienced by each participant over the length of

the study. The authors of two studies supplied us with the data in this format (Salvador 2012; Svanberg 2007), and another author supplied us with incidence data, but on multiple assessment days (Askarifar 2015). We decided to use the data on the day with the highest incidence of grades > 0 (day 7) because, in this study, this probably most closely equates to the maximum score experienced per participant (as reported in the majority of other studies in the meta-analyses). For the other study reporting incidence data (Katranci 2012), but on multiple assessment days, we received no response from the authors, so we again used the data on the day with the highest incidence of grades > 0 (day 14), although we are not sure how valid this is because there was still a high incidence of severe oral mucositis at day 21. For mean scores on multiple assessment days, we used the day with the highest control group mean and recorded the results in an additional table.

The majority of studies assessed oral mucositis at multiple timepoints over approximately four weeks (Cascinu 1994; Gori 2007; Lilleby 2006; Mahood 1991; Rocke 1993; Sorensen 2008; Toro 2013), with some assessing it at multiple timepoints over three weeks (Askarifar 2015; Heydari 2012; Katranci 2012; Svanberg 2007), and the remaining studies assessing it at multiple timepoints over 10 to 14 days (Kakoei 2013; Salvador 2012; Zhang 2011). Where participants had multiple cycles of treatment, we only reported the results for the first cycle.

When studies reported oral mucositis data assessed separately by physicians and participants, we generally chose to use the physician-judgement as we felt that this may be the more objective of the two, and therefore potentially less biased. There was one exception where only the participant-judged data was reported in the study as there was no significant difference between that and the physician-judgement (Sorensen 2008).

To summarise, we were able to include the primary outcome data for 13 of the included studies: 11 in the comparison of cryotherapy versus control (Askarifar 2015; Cascinu 1994; Gori 2007; Heydari 2012; Katranci 2012; Lilleby 2006; Mahood 1991; Salvador 2012; Sorensen 2008; Svanberg 2007; Toro 2013); one in the comparison of different durations of cryotherapy (Rocke 1993); and one in the comparison of cryotherapy versus leucovorin rinses (Zhang 2011).

Secondary outcomes

Interruptions to cancer treatment

No studies reported this important outcome, but the authors of one study responded to our email request and provided us with both dichotomous (event) data and continuous data, the latter in the form of 'days of interruption' (Heydari 2012).

Oral pain

Four studies reported oral pain (Kakoei 2013; Lilleby 2006; Salvador 2012; Svanberg 2007), another study measured oral pain but the study report is currently being written and the data are undergoing analysis (Toro 2013), and the authors of a further study responded to our email request and provided us with oral pain data (Heydari 2012). Only two of these five studies reported data that we were able to combine in a meta-analysis (Lilleby 2006; Salvador 2012), which was the mean oral pain score on a 0 to 10 scale for the study period. Another study also measured oral pain on a 0 to 10 scale, but did not report any usable data in the form of mean and standard deviation for the study period (Svanberg 2007). One study reported mean pain scores on multiple assessment days but did not describe the scale used, and therefore we were unable to use the data for meta-analysis (Kakoei 2013). The authors of one study provided us with data measured on a 1 to 5 scale representing the duration of time for which pain was experienced, unlike the other studies where the score represented pain intensity (Heydari 2012). We decided to present these data in an additional table. It is not clear what scale was used in the remaining study for which the data are not yet available (Toro 2013).

Quality of life

No studies reported this outcome. The authors of one study have confirmed that quality of life was measured using the Patient-Reported Oral Mucositis Symptom (PROMS) scale, but the data are currently unavailable as the study report and analysis have not yet been completed (Toro 2013).

Normalcy of diet

Two studies reported the duration, measured in days, of total parenteral nutrition (TPN) (Lilleby 2006; Svanberg 2007). However, one of these studies reported a median and range for each group, rather than mean and standard deviation, so we were unable to use the data in our analysis (Lilleby 2006). Another study reported the functional intake of food and fluids on a 1 to 5 scale, but we were unable to use the data that were presented in a mixed-effect regression model (Salvador 2012).

Adverse events

It was difficult to assess adverse effects in many cases due to the difficulty to distinguish between effects caused by oral cryotherapy and those caused by various cancer treatments. It also did not make sense to formally meta-analyse data from comparisons of oral cryotherapy with no treatment. Furthermore, in the context of cancer treatment, and with no serious effects being expected from sucking ice, we considered this outcome to be of limited importance in this particular review (whereas it may be more important in our reviews of other potentially more harmful interventions for preventing oral mucositis e.g. growth factors and cytokines). We therefore decided to report this outcome in a narrative format.

Four studies did not mention adverse effects (Askarifar 2015; Gori 2007; Kakoei 2013; Zhang 2011), whilst the quality of reporting for this outcome varied between the remaining nine studies.

Number of days in hospital

Three studies reported this outcome (Lilleby 2006; Salvador 2012; Svanberg 2007). We were able to combine the data for two studies, but the third study reported the median and range for each group, and we were therefore unable to use the data (Lilleby 2006).

Number of days of treatment with opioid analgesics

Two studies reported this outcome (Lilleby 2006; Svanberg 2007), but one reported the median and range for each group, and we were therefore unable to use the data (Lilleby 2006). A further study has measured 'narcotic use' but the data are currently unavailable as the study report and analysis have not yet been completed, and we do not know how this outcome was measured (Toro 2013).

Number of days unable to take medicine orally

No studies reported this outcome.

Excluded studies

We excluded 11 studies from this review for the following reasons.

- Not a randomised controlled trial (RCT): non-random allocation to groups (Karagozoglu 2005; Papadeas 2007; Sato 2006); used historical controls (Aisa 2005; Mori 2006); translation to English confirmed it was case series (Ohyama 1994).
- Unclear if RCT and authors have not provided clarification (Sato 1997).
- Cross-over study with no reporting of first-period data (Baydar 2005; Castelino 2011; Nikoletti 2005).
- Confounding due to co-interventions and therefore not possible to attribute effect to cryotherapy (de Paula Eduardo 2014).

Risk of bias in included studies

Allocation

Random sequence generation

Eight studies described an adequate method of random sequence generation (Askarifar 2015; Gori 2007; Heydari 2012; Kakoei 2013; Katranci 2012; Salvador 2012; Svanberg 2007; Zhang 2011), and the authors of three further studies responded to our requests for further information (Cascinu 1994; Lilleby 2006; Toro 2013), which clarified that their methods were adequate. Therefore we assessed 11 studies as being at low risk of bias for this domain. The remaining three studies only stated that participants were randomised but did not describe their methods, so they were assessed as being at unclear risk of bias for this domain (Mahood 1991; Rocke 1993; Sorensen 2008).

Allocation concealment

Two studies provided details of how the random sequence was concealed from those involved in the study (Salvador 2012; Svanberg 2007), with a further five studies providing details through correspondence (Askarifar 2015; Cascinu 1994; Heydari 2012; Lilleby 2006; Toro 2013). Therefore we assessed seven studies as being at low risk of bias for this domain. The remaining seven studies did not mention any methods used to conceal the random sequence, and we assessed them as being at unclear risk of bias (Gori 2007; Kakoei 2013; Katranci 2012; Mahood 1991; Rocke 1993; Sorensen 2008; Zhang 2011).

Overall, seven studies are at low risk of selection bias, meaning that we assessed both of the above domains as being at low risk of bias (Askarifar 2015; Cascinu 1994; Heydari 2012; Lilleby 2006; Salvador 2012; Svanberg 2007; Toro 2013). The remaining seven studies are at unclear risk of selection bias because one or both of the above domains were rated as unclear (Gori 2007; Kakoei 2013; Katranci 2012; Mahood 1991; Rocke 1993; Sorensen 2008; Zhang 2011).

Blinding

Blinding of participants and personnel (performance bias)

It is not possible to blind participants or personnel to whether or not oral cryotherapy has been allocated. Knowledge of treatment allocation could affect expectations and behaviours (e.g. control group participants may take other interventions). Therefore we judged all 14 studies to be at high risk of performance bias.

Blinding of outcome assessment (detection bias)

The subjective elements involved in the World Health Organisation (WHO) and National Cancer Institute common toxicity criteria (NCI-CTC) tools, which were used to measure oral mucositis in the studies included in this review (Appendix 8), require the patient's assessment of pain/soreness and their ability to swallow. Even if blinding of outcome assessment is attempted, we do not believe it is feasible. Therefore we judged all 14 studies to be at high risk of detection bias.

Incomplete outcome data

Only two studies were at high risk of attrition bias (Askarifar 2015; Sorensen 2008), both due to differential attrition between groups, which may have been linked to prognosis. The remaining 12 studies had negligible or no attrition and we assessed them as being at low risk of attrition bias.

Selective reporting

Three studies were at high risk of selective reporting bias. One of these studies reported oral pain, which was not stated in the trials registry record or the methods section of the study report (Kakoei 2013). It is possible that the decision to report this outcome was based on statistical significance. Another study stated only that there was no significant differences for oral pain, but reported no data (Svanberg 2007). The remaining study only reported the incidence of each grade of oral mucositis on day 4, despite stating that it was measured on the day of chemotherapy and day 10 (Zhang 2011). We assessed the other 11 studies as being at low risk of selective reporting bias as we could detect no obvious problems.

Other potential sources of bias

We did not consider there to be any issues arising from other potential sources of bias in any of the studies and we therefore assessed them all as being at low risk of bias for this domain.

Overall risk of bias

All fourteen studies were assessed as being at high overall risk of bias (Figure 1).

Effects of interventions

See: **Summary of findings for the main comparison** Cryotherapy versus control for preventing oral mucositis in adults receiving fluorouracil-based treatment for solid cancers; **Summary of findings 2** Cryotherapy versus control for preventing oral mucositis in adults receiving high-dose melphalan-based treatment prior to haematopoietic stem cell transplantation for haematological cancers

Comparison 1: Cryotherapy versus control (standard care or no treatment)

Oral mucositis (any)

Fluorouracil (5FU) treatment for solid cancers

Five studies (Cascinu 1994; Heydari 2012; Katranci 2012; Mahood 1991; Sorensen 2008), all at high risk of bias and analysing 444 participants, were combined in a meta-analysis which showed that oral cryotherapy reduced the risk of developing oral mucositis (risk ratio (RR) 0.61, 95% confidence interval (CI) 0.52 to 0.72, P < 0.00001) when compared to control (Analysis 1.1). There was

no heterogeneity in this effect estimate (I^2 = 0%). This can be interpreted as a 39% (95% CI 28% to 48%) reduction in the risk of developing oral mucositis associated with oral cryotherapy. Or in other words, 4 people (95% CI 3 to 5 people) would need to receive oral cryotherapy in order to prevent one additional person from developing oral mucositis.

High-dose melphalan-based treatment prior to stem cell transplantation

Five studies (Askarifar 2015; Lilleby 2006; Salvador 2012; Svanberg 2007; Toro 2013), all at high risk of bias and analysing 270 participants, were combined in a meta-analysis. There is evidence to show that oral cryotherapy reduced the risk of developing oral mucositis (RR 0.59, 95% CI 0.35 to 1.01, P = 0.05) when compared to control (Analysis 1.1). Oral cryotherapy reduced the risk of developing oral mucositis by 41% although the uncertainty surrounding this effect estimate means that the 95% CI ranges from a 65% reduction to a 1% increase in risk. We would need to treat 3 people with oral cryotherapy to prevent one additional person from developing oral mucositis. The confidence interval ranges from 2 people needing to receive oral cryotherapy to prevent one additional person from developing oral mucositis, to 111 people needing to receive oral cryotherapy for one additional person to develop oral mucositis. There was considerable heterogeneity associated with this effect estimate (I^2 = 95%), although the reason/s for this inconsistency is/are not clear on investigation of the characteristics of the studies, in terms of the participants, settings, methods, and interventions.

Methotrexate treatment post-stem cell transplantation to prevent graft versus host disease

One study (Gori 2007), at high risk of bias and analysing 122 participants, showed that there is insufficient evidence to determine whether or not oral cryotherapy reduces the risk of developing oral mucositis (RR 0.98, 95% CI 0.90 to 1.07, P = 0.73) when compared to control (Analysis 1.1).

Radiotherapy to the head and neck

One study (Kakoei 2013), at high risk of bias and analysing 40 participants, showed that there is insufficient evidence to determine whether or not oral cryotherapy reduces the mean severity of oral mucositis 14 days after radiotherapy (mean difference (MD) -0.25, 95% CI -0.72 to 0.22, P = 0.29) when compared to control (Additional Table 1).

Oral mucositis (moderate to severe)

Fluorouracil (5FU) treatment for solid cancers

The same five studies (Cascinu 1994; Heydari 2012; Katranci 2012; Mahood 1991; Sorensen 2008), when combined, showed that oral cryotherapy reduced the risk of developing moderate to severe oral mucositis (RR 0.52, 95% CI 0.41 to 0.65, P < 0.00001) when compared to control (Analysis 1.2). There was no heterogeneity (I^2 = 0%). Oral cryotherapy reduced the risk of developing moderate to severe oral mucositis by 48% (95% CI 35% to 59%). We would need to treat 4 people (95% CI 4 to 6 people) with oral cryotherapy in order to prevent one additional person from developing moderate to severe oral mucositis.

High-dose melphalan-based treatment prior to stem cell transplantation

The same five studies (Askarifar 2015; Lilleby 2006; Salvador 2012; Svanberg 2007; Toro 2013), when combined, showed that there is evidence to show that oral cryotherapy reduced the risk of developing moderate to severe oral mucositis (RR 0.43, 95% CI 0.17 to 1.09, P = 0.07) when compared to control (Analysis 1.2). Oral cryotherapy reduced the risk of developing moderate to severe oral mucositis by 57% although the uncertainty surrounding this effect estimate means that the 95% CI ranges from a 83% reduction to a 9% increase in risk. We would need to treat 3 people with oral cryotherapy to prevent one additional person from developing moderate to severe oral mucositis. The confidence interval ranges from 2 people needing to receive oral cryotherapy to prevent one additional person from developing moderate to severe oral mucositis, to 17 people needing to receive oral cryotherapy for one additional person to develop moderate to severe oral mucositis. There was considerable heterogeneity associated with this effect estimate (I^2 = 92%), although the reason/s for this inconsistency is/are not clear on investigation of the characteristics of the studies, in terms of the participants, settings, methods, and interventions.

Methotrexate treatment post-stem cell transplantation to prevent graft versus host disease

The same study (Gori 2007) showed that there is insufficient evidence to determine whether or not oral cryotherapy reduces the risk of developing moderate to severe oral mucositis (RR 1.01, 95% CI 0.85 to 1.20, P = 0.93) when compared to control (Analysis 1.2).

Radiotherapy to the head and neck

The study in this subgroup did not assess this outcome.

Oral mucositis (severe)

Fluorouracil (5FU) treatment for solid cancers

The same five studies (Cascinu 1994; Heydari 2012; Katranci 2012; Mahood 1991; Sorensen 2008), when combined, showed that oral cryotherapy reduced the risk of developing severe oral mucositis (RR 0.40, 95% CI 0.27 to 0.61, P < 0.0001) when compared to control (Analysis 1.3). There was no heterogeneity (I^2 = 0%). Oral cryotherapy reduced the risk of developing severe oral mucositis by 60% (39% to 73%). We would need to treat 6 people (95% CI 5 to 9 people) with oral cryotherapy to prevent one additional person from developing severe oral mucositis.

High-dose melphalan-based treatment prior to stem cell transplantation

The same five studies (Askarifar 2015; Lilleby 2006; Salvador 2012; Svanberg 2007; Toro 2013), when combined, showed that oral cryotherapy reduced the risk of developing severe oral mucositis (RR 0.38, 95% CI 0.20 to 0.72, P = 0.003) when compared to control (Analysis 1.3). Oral cryotherapy reduced the risk of developing severe oral mucositis by 62% (95% CI 28% to 80%). We would need to treat 4 people (95% CI 3 to 9 people) with oral cryotherapy to prevent one additional person from developing severe oral mucositis. There was moderate amount of heterogeneity associated with this effect estimate (I^2 = 42%), although the reason/s for this inconsistency is/are not clear on investigation of the characteristics of the studies, in terms of the participants, settings, methods, and interventions.

Methotrexate treatment post-stem cell transplantation to prevent graft versus host disease

The same study (Gori 2007) showed that there is insufficient evidence to determine whether or not oral cryotherapy reduces the risk of developing moderate to severe oral mucositis (RR 0.88, 95% CI 0.61 to 1.25, P = 0.47) when compared to control (Analysis 1.3).

Radiotherapy to the head and neck

The study in this subgroup did not assess this outcome.

Interruptions to cancer treatment

Fluorouracil (5FU) treatment for solid cancers

One study (Heydari 2012), at high risk of bias and analysing 80 participants, showed that oral cryotherapy reduced the risk of treatment interruption (RR 0.44, 95% CI 0.20 to 0.95, P = 0.04) when compared to control (Analysis 1.4). In other words, oral cryotherapy reduced the risk of treatment interruption by 56% (95% CI 5% to 80%). We would need to treat 5 people (95% 4 to 50 people) with oral cryotherapy in order to prevent one additional person from having a treatment interruption. The uncertainty, due to the single study with a small number of participants, surrounding this effect estimate is reflected by the wide range in the confidence interval.

The same study showed that oral cryotherapy reduced the duration of treatment interruption by eight days (95% CI 9.26 to 6.74 days, P < 0.00001) when compared to control (Analysis 1.5).

High-dose melphalan-based treatment prior to stem cell transplantation

No studies in this subgroup assessed this outcome.

Graft versus host disease prophylaxis

The study in this subgroup did not assess this outcome.

Radiotherapy to the head and neck

The study in this subgroup did not assess this outcome.

Oral pain

Fluorouracil (5FU) treatment for solid cancers

One study (Heydari 2012), at high risk of bias and analysing 80 participants, showed that oral cryotherapy reduced the duration of oral pain experience (MD -1.93, 95% CI -2.37 to -1.49, P < 0.00001) when compared to control (Additional Table 1). The 1 to 5 scale used to measure this outcome makes it impossible to accurately interpret this result in any meaningful way.

High-dose melphalan-based treatment prior to stem cell transplantation

Two studies (Lilleby 2006; Salvador 2012), both at high risk of bias and analysing 85 participants, showed that oral cryotherapy reduced the intensity of oral pain (MD -1.50, 95% CI -2.11 to -0.89, P < 0.00001) when compared to control (Analysis 1.6). There was a negligible amount of heterogeneity associated with this effect estimate (I^2 = 4%). This result represents a 70% reduction in oral pain but this figure may be misleading as there was only a 1.5 point reduction on a 0 to 10 scale.

Graft versus host disease prophylaxis

The study in this subgroup did not assess this outcome.

Radiotherapy to the head and neck

The study in this subgroup assessed oral pain but did not report details of the scale used, so we were unable to use the data.

Quality of life

Fluorouracil (5FU) treatment for solid cancers

No studies in this subgroup assessed this outcome.

High-dose melphalan-based treatment prior to stem cell transplantation

One study assessed this outcome but the data are currently unavailable as the study report and analysis have not yet been completed (Toro 2013).

Graft versus host disease prophylaxis

The study in this subgroup did not assess this outcome.

Radiotherapy to the head and neck

The study in this subgroup did not assess this outcome.

Normalcy of diet

Fluorouracil (5FU) treatment for solid cancers

No studies in this subgroup assessed this outcome.

High-dose melphalan-based treatment prior to stem cell transplantation

One study, at high risk of bias and analysing 78 participants (Svanberg 2007), showed that oral cryotherapy reduced the duration of total parenteral nutrition by 2.18 days (95% CI 0.03 to 4.33 days, P = 0.05) when compared to control (Analysis 1.7).

A further study, at high risk of bias and analysing 40 participants (Lilleby 2006), reported that oral cryotherapy reduced the number of days of total parenteral nutrition (Additional Table 1).

Graft versus host disease prophylaxis

The study in this subgroup did not assess this outcome.

Radiotherapy to the head and neck

The study in this subgroup did not assess this outcome.

Adverse events

Fluorouracil (5FU) treatment for solid cancers

One study reported that there were no adverse effects ("problems") (Katranci 2012), whilst the other four studies reported low rates of very minor adverse events (headache, chills, numbness/taste disturbance).

High-dose melphalan-based treatment prior to stem cell transplantation

One study did not report adverse events (Askarifar 2015), whilst another informed us by email that there were "no serious adverse events" (Toro 2013). The remaining two studies reported only low rates of shooting pain from the teeth (Svanberg 2007), and coldness (Lilleby 2006). In the latter study, this stopped some participants from continuing the cryotherapy regimen, although this is not surprising as they were required to hold ice in their mouths continuously for a total of seven hours.

Graft versus host disease prophylaxis

The study in this subgroup did not report on adverse events.

Radiotherapy to the head and neck

The study in this subgroup did not report on adverse events. However, we assume that there were none because the participants only had to hold ice in their mouth for 5-minute periods.

Number of days in hospital

Fluorouracil (5FU) treatment for solid cancers

No studies in this subgroup assessed this outcome.

High-dose melphalan-based treatment prior to stem cell transplantation

Two studies (Salvador 2012; Svanberg 2007), both at high risk of bias and analysing 123 participants, were combined in a meta-analysis with no heterogeneity (I^2 = 0%). There is insufficient evidence to show that oral cryotherapy reduces the duration of hospitalisation (MD -1.39 days, 95% CI -2.97 to 0.19 days, P = 0.09) when compared to control (Analysis 1.8).

A further study, at high risk of bias and analysing 40 participants (Lilleby 2006), reported that there was insufficient evidence to show a reduction in the duration of hospitalisation (Additional Table 1).

Graft versus host disease prophylaxis

The study in this subgroup did not assess this outcome.

Radiotherapy to the head and neck

The study in this subgroup did not assess this outcome.

Number of days of treatment with opioid analgesics

Fluorouracil (5FU) treatment for solid cancers

No studies in this subgroup assessed this outcome.

High-dose melphalan-based treatment prior to stem cell transplantation

One study (Svanberg 2007), at high risk of bias and analysing 78 participants, showed that there is insufficient evidence to determine whether or not oral cryotherapy reduces the duration of opioid use (MD -2.28 days, 95% CI -5.33 to 0.77 days, P = 0.14) when compared to control (Analysis 1.9).

A further study (Lilleby 2006), at high risk of bias and analysing 40 participants, reported that oral cryotherapy reduced the duration of opioid use (Additional Table 1).

Graft versus host disease prophylaxis

The study in this subgroup did not assess this outcome.

Radiotherapy to the head and neck

The study in this subgroup did not assess this outcome.

Number of days unable to take medicine orally

Fluorouracil (5FU) treatment for solid cancers

No studies in this subgroup assessed this outcome.

High-dose melphalan-based treatment prior to stem cell transplantation

No studies in this subgroup assessed this outcome.

Graft versus host disease prophylaxis

The study in this subgroup did not assess this outcome.

Radiotherapy to the head and neck

The study in this subgroup did not assess this outcome.

Comparison 2: Different oral cryotherapy regimens

One study (Rocke 1993), at high risk of bias and analysing 178 participants having treatment for solid cancer (fluorouracil and leucovorin), showed that there is insufficient evidence to determine whether or not the risk of developing oral mucositis is different when using 30 minutes or 60 minutes of oral cryotherapy (RR 0.89, 95% CI 0.62 to 1.29, P = 0.54) (Analysis 2.1).

The results were similar for the risk of developing moderate to severe oral mucositis (RR 0.68, 95% CI 0.36 to 1.30, P = 0.25) (Analysis 2.2), and severe oral mucositis (RR 0.60, 95% CI 0.23 to 1.58, P = 0.30) (Analysis 2.3).

The study in this comparison did not assess any other outcomes of this review.

Comparison 3: Cryotherapy versus chlorhexidine

One study (Sorensen 2008), at high risk of bias and analysing 133 participants having treatment for solid cancer (fluorouracil and leucovorin), showed that there is insufficient evidence to determine whether or not the risk of developing oral mucositis is different when using oral cryotherapy or chlorhexidine rinse (RR 0.97, 95% CI 0.71 to 1.32, P = 0.84) (Analysis 3.1).

The results were similar for the risk of developing moderate to severe oral mucositis (RR 0.89, 95% CI 0.51 to 1.56, P = 0.68) (Analysis 3.2), and severe oral mucositis (RR 0.86, 95% CI 0.34 to 2.18, P = 0.76) (Analysis 3.3).

The study in this comparison did not assess any other outcomes of this review.

Comparison 4: Cryotherapy versus low-dose leucovorin versus high-dose leucovorin

One study (Zhang 2011), at high risk of bias and analysing 147 participants having treatment for solid (osteosarcoma) cancer (high-dose methotrexate, vincristine and leucovorin), showed that oral cryotherapy reduced the risk of developing oral mucositis when compared to both low-dose leucovorin rinse (RR 0.67, 95% CI 0.50 to 0.90, P = 0.008) and high-dose leucovorin rinse (RR 0.65, 95% CI 0.47 to 0.90, P = 0.01) (Analysis 4.1).

There was insufficient evidence to determine whether or not the risk of developing moderate to severe oral mucositis is different when using oral cryotherapy or low-dose leucovorin rinse (RR 0.18, 95% CI 0.01 to 3.42, P = 0.25), or when using oral cryotherapy compared to high-dose leucovorin rinse (not estimable - no participants had developed moderate or severe oral mucositis by the fourth day after chemotherapy when the data were reported) (Analysis 4.2).

There was insufficient evidence to determine whether or not the risk of developing severe oral mucositis is different when using oral cryotherapy compared to either low-dose or high-dose leucovorin rinse (Analysis 4.3). No participants had developed severe oral mucositis by the fourth day after chemotherapy when the data were reported.

The study in this comparison did not assess any other outcomes of this review.

Compliance

Two studies did not report on compliance (Askarifar 2015; Zhang 2011). The remaining studies reported a high degree of compliance, with the large majority of participants managing to keep their mouths constantly cooled.

DISCUSSION

Summary of main results

Fourteen randomised controlled trials (RCTs) met our eligibility criteria and were included in this review. We assessed the body of evidence for each comparison and outcome using GRADE methodology (GRADE 2004). Most of the evidence we found relates to the comparison of oral cryotherapy versus a control group of standard care or no treatment in adult patients. We only present a 'Summary of findings' table where we were able to perform a meta-analysis for the main outcomes, thus we produced two separate tables for: 1) evidence for participants receiving fluorouracil-based (5FU) treatment for solid cancers (Summary of findings for the main comparison); and 2) evidence for participants receiving high-dose melphalan-based cancer treatment prior to haematopoietic stem cell transplantation (HSCT) (Summary of findings 2).

Our main findings are as follows.

Adults receiving 5FU-based treatment for solid cancers

- Oral cryotherapy probably reduces oral mucositis of all severities (moderate quality evidence).
- There is some weak evidence that oral cryotherapy reduces both the incidence of treatment interruptions and the duration of treatment interruptions (very low quality evidence).
- There is some weak evidence that oral cryotherapy reduces the duration of pain experience (very low quality evidence).

Adults receiving high-dose melphalan prior to HSCT

- Oral cryotherapy may reduce the incidence of both oral mucositis (any severity versus none) and moderate to severe oral mucositis (low quality evidence), and probably does reduce the incidence of severe oral mucositis (moderate quality evidence).
- Oral cryotherapy may lead to a small reduction in oral pain (low quality evidence).
- There is some weak evidence that oral cryotherapy reduces the duration of total parenteral nutrition (TPN) (very low quality evidence).
- There is insufficient evidence to determine whether or not oral cryotherapy reduces the number of days in hospital (low quality evidence).
- There is insufficient evidence to determine whether or not oral cryotherapy reduces the number of days of treatment with opioid analgesics (very low quality evidence).

There is insufficient evidence to determine the effects of oral cryotherapy in: a) people receiving low-dose methotrexate for preventing graft-versus-host disease (GVHD) after HSCT; and b) people receiving head and neck radiotherapy (both very low quality evidence).

For the other comparisons included in this review, there was only very low quality evidence provided by single studies. In participants receiving 5FU-based treatment for solid cancers, there is insufficient evidence to determine whether or not there is a difference between: a) 30 minutes and 60 minutes of oral cryotherapy; or b) oral cryotherapy and chlorhexidine rinse, for reducing the risk of developing any severity of oral mucositis. In participants receiving high-dose methotrexate, vincristine and leucovorin for bone cancer (osteosarcoma), there is some weak evidence that oral cryotherapy reduces the risk of developing oral mucositis when compared to leucovorin rinses.

Oral cryotherapy is safe, with low rates of very minor adverse effects, which ensures that compliance with this therapy is generally high.

Overall completeness and applicability of evidence

We have found evidence which partially answers the review question of whether or not oral cryotherapy can prevent oral mucositis in cancer patients who are receiving treatment. We have enough evidence to answer this question for adults receiving 5FU-based treatment for solid cancers in a satisfactory manner. However, for adults with haematological cancers receiving melphalan-based cancer treatment prior to HSCT, the evidence is not complete and may be difficult to apply to different settings due to conflicting results amongst the individual studies. We would welcome more evidence in this group of patients and in a variety of settings. There is also very limited evidence on people receiving chemotherapy as GVHD prophylaxis, and also people receiving radiotherapy, whilst there is no RCT evidence on people receiving targeted therapy. The rationale behind the biological plausibility for using oral cryotherapy in cancer patients receiving chemotherapy has been explained in the literature. However, this is not the case for patients receiving radiotherapy to the head and neck or targeted therapy, which makes it difficult to determine the procedure (i.e. when and for how long to perform cryotherapy), yet it is still worth further investigation if there is a chance that this simple intervention can help these patients.

There is no evidence on the effects of this intervention in children, perhaps because it may be considered unfeasible to expect children to hold ice in their mouths for long periods of time, due to the discomfort caused. However, as demonstrated in some of the studies included in this review, there are alternatives to holding crushed ice or ice chips or ice cubes in the mouth, such as the use of iced water/drinks or ice lollies/popsicles. It is also possible that ice chips or cubes may be a potential choking hazard in children.

There is also a lack of evidence on the effects of oral cryotherapy in low-income and lower-middle-income countries.

Quality of the evidence

We included 14 RCTs that analysed 1280 participants. The body of evidence that we identified on adults receiving 5FU-based treatment for solid cancers allows a fairly robust conclusion to be made about the effects of oral cryotherapy for reducing the risk of oral mucositis in that group of patients. That is to say we can be quite confident in the results and we therefore assessed the evidence as being of moderate quality. We downgraded the rating of the evidence by one level due to the lack of blinding of participants, personnel and outcome assessors. Lack of blinding of participants and personnel in these studies is an unavoidable problem and does not necessarily reflect the 'quality' in terms of whether or not the studies were well conducted, although it does affect the risk of bias, which we must account for in our assessment of the quality of the body of evidence. Future studies may avoid the risk of detection bias by using a more objective measurement tool for the assessment of oral mucositis. However, this would affect our ability to combine the new studies in meta-analyses with the current published studies that all use either the WHO or NCI-CTC tools, which incorporate subjective elements.

The body of evidence that we identified on adults receiving high-dose melphalan-based cancer treatment prior to HSCT does not allow for such robust conclusions for the outcomes 'any mucositis' and 'moderate to severe mucositis'. There were the same problems with risk of bias as discussed above, and also inconsistency in the results of the individual studies, and we therefore downgraded our rating of the quality of the body of evidence by two levels, resulting in low quality evidence. Although we would conclude that oral cryotherapy may be beneficial in this group of patients, the results were very uncertain, with wide confidence intervals, and even the possibility of a slight increase in the risk of developing any or moderate to severe mucositis. However, we did not downgrade for precision as the upper confidence limits did not include appreciable harm, and also because we do not consider it to be very low quality evidence. The evidence for oral cryotherapy reducing the risk of severe oral mucositis in this group of patients was more robust, resulting in moderate quality evidence.

We did not downgrade either of the above bodies of evidence for indirectness resulting from the studies only being conducted on adults. However, there is some evidence that, with some diseases, children have more toxicity than adults who receive the same chemotherapy regimens (Juergens 2006). Therefore, it is possible that results in adults are not directly applicable to children, who may metabolise drugs differently and therefore experience different toxicity severity.

There was insufficient evidence, of very low quality, on the effects of oral cryotherapy for reducing the risk of oral mucositis to allow any conclusions to be made for people receiving chemotherapy as GVHD prophylaxis, and also people receiving radiotherapy. This was downgraded for risk of bias, imprecision and indirectness, the latter because they were single study subgroups and were not replicated in any other settings. There was no evidence relating to children-only.

It was unfortunate that there was such limited evidence on the secondary outcomes of this review. These outcomes, and others, are likely to be important to patients and clinicians, and this serves to highlight the importance of core outcomes sets such as the one published by Bellm et al (Bellm 2002). We would urge future trialists to utilise such outcome sets in order to standardise what is measured and how it is measured, so as to maximise the usefulness of data produced by the randomisation of people, and thus reduce research waste.

Potential biases in the review process

We attempted to minimise biases in the review process but we cannot discount the fact that it is affected by other biases. For example, there were two studies that presented oral mucositis incidence data on multiple days rather than our preferred format of presenting a maximum score experienced per participant over the whole study period (Askarifar 2015; Katranci 2012). Rather than lose important data, we decided to present the data from the day on which the incidence of grades higher than 0 was highest. We chose this method with the intention of equating to the maximum score experience, though we acknowledge this is not ideal and may not equate accurately enough. Another decision we made was to exclude studies where the participants received oral cryotherapy plus another intervention, even if the control group also received the other intervention. For example, one study that we excluded compared oral cryotherapy plus laser therapy versus laser therapy (de Paula Eduardo 2014). We could not exclude the possibility of interaction between the interventions and therefore we would not be confident in stating that any effect was due to the cryotherapy. However, in some of the studies, both groups received standard care, with the intervention group also receiving oral cryotherapy. We felt that this was a different situation because the standard care involved things like advice and education on mouth care, or mouth rinsing with saline, none of which would interact with the cryotherapy in a way that could bias the results.

Agreements and disagreements with other studies or reviews

A recent meta-analysis conducted in China on oral cryotherapy for preventing oral mucositis in patients with haematological cancers undergoing HSCT (Wang 2015), concluded that oral cryotherapy reduces the incidence of severe oral mucositis (risk ratio (RR) 0.52, 95% confidence interval 0.27 to 0.99). This was a smaller reduction than we calculated (RR 0.38, 95% CI 0.20 to 0.72), but they included one study that we excluded due to the possibility of confounding (de Paula Eduardo 2014), another study that we did not include in this subgroup due to treatment differences (Gori 2007), and another study that we have been unable to obtain the data for, which is currently listed in Characteristics of studies awaiting classification (Lu 2013). We included two studies that the Chinese authors did not include, for which we managed to obtain data through correspondence with the study authors (Askarifar 2015; Salvador 2012). The Chinese authors were also in agreement with our results on 'duration of opioid use' and 'days of TPN', although they included data from Lilleby 2006, which reported medians and ranges for some of our outcomes, and it was not clear what methods they used to include this study in the meta-analyses. The inclusion of Lilleby 2006 data in their meta-analysis for the outcome 'duration of hospitalisation' resulted in a significant result in favour of oral cryotherapy, in contrast to our result which did not achieve significance.

Our results strongly support the conclusions of another systematic review of oral cryotherapy that was carried out by the Mucositis Study Group (MSG) of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/

ISOO), and that is not limited to RCTs (Peterson 2013). This review feeds into the 'MASCC/ISOO Clinical Practice Guidelines for the Management of Mucositis Secondary to Cancer Therapy (Lalla 2014). Specifically, the guidance from this group is currently as follows.

- Recommendations in favour of an intervention (i.e. strong evidence supporting effectiveness): The panel *recommends* that 30 minutes of oral cryotherapy be used to *prevent* oral mucositis in patients receiving bolus 5FU chemotherapy (level II evidence).
- Suggestions in favour of an intervention (i.e. weaker evidence supporting effectiveness): The panel *suggests* that oral cryotherapy be used to *prevent* oral mucositis in patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for HSCT (level III evidence).

This guidance is perhaps further strengthened by our Cochrane systematic review, as we have included new data/evidence not included in the MASCC/ISOO review or guidelines, yet the conclusions remain the same. It could even be argued that, due to the new data included in our two subgroups of patients matching those above, the level of evidence would now be level I for patients receiving bolus 5FU chemotherapy, and level I or II for patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for HSCT. Level I evidence is "evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power)" (Lalla 2014). There are now five RCTs in our 5FU subgroup with sufficient power to give a clear and fairly precise result. Our melphalan subgroup also now has five RCTs, but with fewer participants, giving a less precise result. However, the evidence for prevention of severe oral mucositis in this subgroup is fairly robust.

AUTHORS' CONCLUSIONS

Implications for practice

We are confident that oral cryotherapy leads to large reductions in the incidence of oral mucositis of all severities in adults receiving fluorouracil-based (5FU) treatment for solid cancers. We are less confident in the ability of oral cryotherapy to reduce the incidence of oral mucositis in adults receiving high-dose melphalan-based cancer treatment prior to haematopoietic stem cell transplantation (HSCT). Evidence suggests that it does reduce oral mucositis in these adults, but we are less certain about the size of the reduction, which could be large or small. However, we are confident that there is an appreciable reduction in severe oral mucositis in these adults.

This Cochrane systematic review has included some very recent and currently unpublished data, and strengthens international guideline statements for adults receiving the above cancer treatments.

Implications for research

It is fairly clear that oral cryotherapy is beneficial for adults receiving 5FU chemotherapy, and therefore further randomised controlled trials (RCTs) are probably not warranted. Instead, it may be better to conduct new head-to-head RCTs comparing oral cryotherapy with other promising preventive treatments such as lasers, growth factors and cytokines, and other interventions.

We need more studies assessing oral cryotherapy in people receiving high-dose melphalan-based cancer treatment prior to HSCT in order to further strengthen the body of evidence reported in this review. Further investigation of the optimum cryotherapy regimen may be warranted in these patients and, as mentioned above, more head-to-head studies. We also need more studies looking at the effects of oral cryotherapy in people receiving other cancer treatments, such as different chemotherapy drugs (including those given as prophylaxis for graft-versus-host disease after HSCT), radiotherapy, and even targeted therapies. Studies of children may also be warranted if this intervention can help them complete their optimum cancer treatment regimens, whilst minimising their pain, discomfort and ability to eat and drink properly.

We urge trialists conducting future RCTs to measure and report all the outcomes, as a minimum, listed in the core outcome set produced by Bellm et al (Bellm 2002). For our primary outcome of oral mucositis, it would be beneficial to use both a measurement tool such as the WHO or NCI-NCT scale (Appendix 8), to allow us to combine the data with those already included in this review, and also an objective scale with blinded outcome assessment, in order to reduce the bias inherent in these studies.

ACKNOWLEDGEMENTS

We would like to thank Laura MacDonald, Tanya Walsh and Sue Furness of the Cochrane Oral Health Group editorial team for their help in preparing this systematic review. We also thank Luisa Fernandez Mauleffinch (Cochrane Oral Health Group) for copy editing the review and Professor Douglas E Peterson (University of Connecticut) for his helpful feedback on both the protocol and full review.

We are grateful to Professor Toru Naito (Fukuoka Dental College, Japan) and Fang Hua (The University of Manchester) for their translations of Japanese and Chinese studies respectively.

Many thanks to the following study authors who provided extra information on their studies.

- Sima Lakdizaji: provided pre-publication copy of study and gave us oral mucositis incidence on days 3, 7, 14 and clarified details on allocation concealment (Askarifar 2015).
- Stefano Cascinu: provided details of random sequence generation and allocation concealment in a previous version of the review (Cascinu 1994).
- Hassan Sharifi: provided details of allocation concealment and provided full data on extra outcomes not reported in the study (Heydari 2012).
- William Bensinger: provided details of random sequence generation and allocation concealment (Lilleby 2006).
- Maria Salvador: provided maximum oral mucositis score experienced by each participant over the length of the study (Salvador 2012).
- Ann-Carin Svanberg: provided maximum oral mucositis score experienced by each participant over the length of the study (Svanberg 2007).
- Juan Toro: completed the characteristics table for this study and provided details of random sequence generation and allocation concealment (Toro 2013).

REFERENCES

References to studies included in this review

Askarifar 2015 *{unpublished data only}*

Askarifar M, Lakdizaji S, Ramzi M, Rahmani A, Jabbarzadeh F. The effect of oral cryotherapy on chemotherapy-induced oral mucositis in patients undergoing autologous transplantation of blood stem cells: a clinical trial. Iranian Red Crescent Medical Journal 2015 [Epub ahead of print].

Cascinu 1994 *{published and unpublished data}*

Cascinu S, Fedeli A, Fedeli SL, Catalano G. Oral cooling (cryotherapy), an effective treatment for the prevention of 5-fluorouracil-induced stomatitis. *European Journal of Cancer. Part B, Oral Oncology* 1994;**30B**(4):234-6.

Gori 2007 *{published data only}*

Gori E, Arpinati M, Bonifazi F, Errico A, Mega A, Alberani F, et al. Cryotherapy in the prevention of oral mucositis in patients receiving low-dose methotrexate following myeloablative allogeneic stem cell transplantation: a prospective randomized study of the Gruppo Italiano Trapianto di Midollo Osseo nurses group. Bone Marrow Transplantation 2007; Vol. 39, issue 6:347-52.

Heydari 2012 *{published and unpublished data}*

Heydari A, Sharifi H, Salek R. Effect of oral cryotherapy on combination chemotherapy-induced oral mucositis: a randomized clinical trial. *Middle East Journal of Cancer* 2012;**3**(2/3):55-64.

Kakoei 2013 *{published data only}*

Kakoei S, Ghassemi A, Nakhaei NR. Effect of cryotherapy on oral mucositis in patients with head and neck cancers receiving radiotherapy. *International Journal of Radiation Research* 2013;**11**(2):117-20.

Katranci 2012 *{published data only}*

Katranci 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):339-44.

Lilleby 2006 *{published and unpublished data}*

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):1031-5.

Mahood 1991 *{published data only}*

Dose AM, Mahood D, Loprinzi CL, Gainey D, Sorensen JM, Therneau T. A controlled trial of oral cryotherapy for preventing stomatitis in patients receiving 5-fluorouracil (5FU) plus leucovorin (LV). A North Central Cancer Treatment Group and Mayo Clinic Study. Proceedings of the 26th Annual Meeting of the American Society of Clinical Oncology; 1990, May 20-22; Washington DC, USA. 1990; Vol. 9:321, Abstract no: 1242.

* Mahood DJ, Dose AM, Loprinzi CL, Veeder MH, Athmann LM, Thereau TM, et al. Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. *Journal of Clinical Oncology* 1991;**9**(3):449-52.

Rocke 1993 *{published data only}*

Rocke LK, Loprinzi CL, Lee JK, Kunselman SJ, Iverson RK, Finck G, et al. A randomized clinical trial of two different durations or oral cryotherapy for prevention of 5-fluorouracil-related stomatitis. *Cancer* 1993;**72**(7):2234-8.

Salvador 2012 *{published and unpublished data}*

Salvador P, Azusano C, Wang L, Howell D. A pilot randomized controlled trial of an oral care intervention to reduce mucositis severity in stem cell transplant patients. *Journal of Pain and Symptom Management* 2012;**44**(1):64-73.

Sorensen 2008 *{published data only}*

Sorensen J, Skovsgaard T, Bork E, Damstrup L, Ingeberg S. Double blind, placebo-controlled randomized study of chlorhexidine prophylaxis for chemotherapy-induced oral mucositis with nonblinded randomized comparison to oral cooling (cryotherapy). *Journal of Clinical Oncology : ASCO annual meeting proceedings* 2006;**24**(18S Part I):470.

* Sorensen JB, Skovsgaard T, Bork E, Damstrup L, Ingeberg S. Double-blind, placebo-controlled, randomized study of chlorhexidine prophylaxis for 5-fluorouracil-based chemotherapy-induced oral mucositis with nonblinded randomized comparison to oral cooling (cryotherapy) in gastrointestinal malignancies. Cancer 2008; Vol. 112, issue 7:1600-6.

Svanberg 2007 *{published and unpublished data}*

* Svanberg A, Birgegard G, Ohrn K. Oral cryotherapy reduces mucositis and opioid use after myeloablative therapy--a randomized controlled trial. Supportive Care in Cancer 2007; Vol. 15, issue 10:1155-61.

Svanberg A, Ohrn K, Birgegård G. Oral cryotherapy reduces mucositis and improves nutrition - a randomised controlled trial. *Journal of Clinical Nursing* 2010;**19**(15-16):2146-51.

Svanberg A, Öhrn K. Cryotherapy during chemotherapy - could it delay or alleviate the development of mucositis?. *Bone Marrow Transplantation* 2004;**33 Suppl 1**:S292.

Toro 2013 *{published and unpublished data}*

* Toro J, Schneider D, Alonzo R, Hasan A, Lee S, Gushiken F, et al. A randomized trial of oral cryotherapy, saline solution and Caphosol for the prevention of high-dose melphalan-induced oral mucositis followed by autologous hematopoietic stem cell transplantation. *Supportive Care in Cancer* 2013;**21**(1 Suppl):S138.

Toro JJ, Schneider D, Alonzo R, Hasan A, Lee S, Gushiken F, et al. A prospective, randomized clinical trial of cryotherapy vs. Supersaturated calcium phosphate rinses vs. Saline rinses for the prevention of oral mucositis in patients with multiple myeloma (MM) receiving high-dose melphalan

(HDM) and autotransplantation. *Biology of Blood and Marrow Transplantation* 2014;**20**(2 Suppl):S204-5.

Toro JJ, Schneider D, Alonzo R, Hasan A, Lee S, Gushiken F, et al. Influence of oral mucositis on the quality of life of patients treated with high-dose melphalan and autologous hematopoietic stem cell transplantation. *Supportive Care in Cancer* 2013;**21**(1 Suppl):S139.

Zhang 2011 *{published data only}*

Zhang W, Li LS, Lu YW, Zhen JC, Zhang XL. Intervention research on preventing oral mucositis after using high dose methotrexate chemotherapy in osteosarcoma by gargling with calcium folinic. *Chinese Pharmaceutical Journal* 2011;**46**(14):1126-8.

References to studies excluded from this review

Aisa 2005 *{published data only}*

Aisa Y, Mori T, Kudo M, Yashima T, Kondo S, Yokoyama A, et al. Oral cryotherapy for the prevention of high-dose melphalan-induced stomatitis in allogeneic hematopoietic stem cell transplant recipients. *Supportive Care in Cancer* 2005;**13**(4):266-9.

Baydar 2005 *{published data only}*

Baydar M, Dikilitas M, Sevinc A, Aydogdu I. Prevention of oral mucositis due to 5-fluorouracil treatment with oral cryotherapy. *Journal of the National Medical Association* 2005;**97**(8):1161-4.

Castelino 2011 *{published data only}*

Castelino F, Devi Elsa S, Jyothi RK. Effectiveness of plain ice cubes versus flavoured ice cubes in preventing oral mucositis associated with injection 5-fluorouracil among cancer patients. *International Journal of Nursing Education Scholarship* 2011;**3**(2):38-40.

de Paula Eduardo 2014 *{published data only}*

de Paula Eduardo F, Bezinelli LM, da Graça Lopes RM, Nascimento Sobrinho JJ, Hamerschlak N, Correa L. Efficacy of cryotherapy associated with laser therapy for decreasing severity of melphalan-induced oral mucositis during hematological stem-cell transplantation: a prospective clinical study. Hematological Oncology 2014 [Epub ahead of print].

Karagozoglu 2005 *{published data only}*

Karagözoğlu S, Filiz Ulusoy M. Chemotherapy: the effect of oral cryotherapy on the development of mucositis. *Journal of Clinical Nursing* 2005;**14**(6):754-65.

Mori 2006 *{published data only}*

Mori T, Yamazaki R, Aisa Y, Nakazato T, Kudo M, Yashima T, et al. Brief oral cryotherapy for the prevention of high-dose melphalan-induced stomatitis in allogeneic hematopoietic stem cell transplant recipients. *Supportive Care in Cancer* 2006;**14**(4):392-5.

Nikoletti 2005 *{published data only}*

Nikoletti S, Hyde S, Shaw T, Myers H, Kristjanson LJ. Comparison of plain ice and flavoured ice for preventing oral mucositis associated with the use of 5 fluorouracil. *Journal of Clinical Nursing* 2005;**14**(6):750-3.

Ohyama 1994 *{published data only}*

Ohyama W, Kano Y, Akutsu M, Tsunoda S. Ice ball cryotherapy for chemotherapy-induced mucositis. *Gan To Kagaku Ryoho* 1994;**21**(15):2675-7.

Papadeas 2007 *{published data only}*

Papadeas E, Naxakis S, Riga M, Kalofonos Ch. Prevention of 5-fluorouracil-related stomatitis by oral cryotherapy: a randomized controlled study. *European Journal Oncology Nursing* 2007;**11**(1):60-5.

Sato 1997 *{published data only}*

Sato A, Kumagai S, Sakaki K, Morikawa H, Song ST, Mori S. Inhibition of 5-fluorouracil-cisplatin-induced stomatitis by oral cryotherapy: use of an ice-bar containing fibrinolysin and deoxyribonuclease comiben (Elase). *Gan To Kagaku Ryoho* 1997;**24**(9):1135-9.

Sato 2006 *{published data only}*

Sato A, Saisho-Hattori T, Koizumi Y, Minegishi M, Iinuma K, Imaizumi M. Prophylaxis of mucosal toxicity by oral propantheline and cryotherapy in children with malignancies undergoing myeloablative chemo-radiotherapy. *The Tohoku Journal of Experimental Medicine* 2006;**210**(4):315-20.

References to studies awaiting assessment

CTRI/2013/08/003906 *{published data only}*

A clinical trial to study the effect of oral ice application in preventing oral ulcer associated with radiotherapy among cancer patients undergoing radiotherapy. www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=6944.

Lu 2013 *{published data only}*

Lu Y, Zhu X, Depei W. Oral cryotherapy for the prevention of mucositis following myeloablative conditioning and hematopoietic stem cell transplantation. *Blood* 2013;**122**(21):5466.

NCT01653106 *{published data only}*

* A randomized study to compare the effect of short- and long-term schedules of cryotherapy on the incidence and severity of mucositis in high-dose melphalan. http://clinicaltrials.gov/show/NCT01653106.

Lamprecht M, Tackett Rn K, Lester J. A randomized study to compare the effect of 2-hour and 6-hour schedules of cryotherapy on the incidence of severe mucositis in high dose melphalan. *Biology of Blood and Marrow Transplantation* 2013;**19**(2 Suppl):S370-1.

Sborov DW, Lamprecht M, Benson D, Tackett K, Efebera YA, Ashley RE, et al. 2-hour cryotherapy effectively reduces severe mucositis associated with high-dose melphalan followed by stem cell rescue: results from a randomized trial. *Blood* 2014;**124**(21):Abstract no: 3960.

Robenolt 2010 *{published data only}*

Robenolt J, Trovato J, Thompson J, Gordon S, de Vera M. Effect of oral cryotherapy on mucositis-related pain and patient functioning in hematopoeitic stem cell transplant recipients

receiving high-dose melphalan. *Biology of Blood and Marrow Transplantation* 2010;**16**(2 Suppl 2):S322.

Xourafas 2009 *{published data only}*

Xourafas V, Heras P, Hatzopoulos A, Karagiannis S. The role of cryotherapy on fentanyl use in breast cancer patients. European Journal of Cancer, Supplement. Proceedings of the Joint ECCO 15 - 34th ESMO Multidisciplinary Congress Berlin Germany. 2009:274.

References to ongoing studies

NCT01789658 *{published data only}*

A randomized controlled trial of cryotherapy for prevention and reduction of severity of oral mucositis in children undergoing hematopoietic stem cell transplantation. http://clinicaltrials.gov/show/NCT01789658.

NCT02326675 *{published data only}*

Randomized controlled, open-label study on the use of cryotherapy in the prevention of chemotherapy-induced mucositis in stem cell transplant patients. http://clinicaltrials.gov/show/NCT02326675.

Additional references

Al-Dasooqi 2013

Al-Dasooqi N, Sonis ST, Bowen JM, Bateman E, Blijlevens N, Gibson RJ, et al. Emerging evidence on the pathobiology of mucositis. *Supportive Care in Cancer* 2013;**21**(11):3233-41.

Bellm 2002

Bellm LA, Cunningham G, Durnell L, Eilers J, Epstein JB, Fleming T, et al. Defining clinically meaningful outcomes in the evaluation of new treatments for oral mucositis: oral mucositis patient provider advisory board. *Cancer Investigation* 2002;**20**(5-6):793-800.

Boers-Doets 2013

Boers-Doets CB, Raber-Durlacher JE, Treister NS, Epstein JB, Arends AB, Wiersma DR, et al. Mammalian target of rapamycin inhibitor-associated stomatitis. *Future Oncology* 2013;**9**(12):1883-92.

Clarke 2007

Clarke M. Standardising outcomes for clinical trials and systematic reviews. *Trials* 2007;**8**:39.

CONSORT 2010

Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery* 2011;**9**(8):672-7.

Dwan 2008

Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS One* 2008;**3**(8):e3081.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

Elting 2008

Elting LS, Keefe DM, Sonis ST, Garden AS, Spijkervet FK, Barasch A, et al. Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. *Cancer* 2008;**113**(10):2704-13.

Epstein 1999

Epstein JB, Emerton S, Kolbinson DA, Le ND, Phillips N, Stevenson-Moore P, et al. Quality of life and oral function following radiotherapy for head and neck cancer. *Head & Neck* 1999;**21**(1):1-11.

GRADE 2004

GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

GRADEpro 2014 [Computer program]

McMaster University. GRADEpro. McMaster University, 2014.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Jensen 2014

Jensen SB, Peterson DE. Oral mucosal injury caused by cancer therapies: current management and new frontiers in research. *Journal of Oral Pathology & Medicine* 2014;**43**(2):81-90.

Juergens 2006

Juergens C, Weston C, Lewis I, Whelan J, Paulussen M, Oberlin O, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. *Pediatric Blood & Cancer* 2006;**47**(1):22-9.

Karagözoğlu 2005

Karagözoğlu S, Filiz Ulusoy M. Chemotherapy: the effect of oral cryotherapy on the development of mucositis. *Journal of Clinical Nursing* 2005;**14**(6):754-65.

Lalla 2008

Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. *Dental Clinics of North America* 2008;**52**(1):61-77.

Lalla 2014

Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 2014;**120**(10):1453-61.

Miller 2001

Miller M, Kearney N. Oral care for patients with cancer: a review of the literature. *Cancer Nursing* 2001;**24**(4):241-54.

Nonzee 2008

Nonzee NJ, Dandade NA, Patel U, Markossian T, Agulnik M, Argiris A, et al. Evaluating the supportive care costs of severe radiochemotherapy-induced mucositis and pharyngitis. *Cancer* 2008;**113**(6):1446-52.

Peterson 2013

Peterson DE, Ohrn K, Bowen J, Fliedner M, Lees J, Loprinzi C, et al. Systematic review of oral cryotherapy for management of oral mucositis caused by cancer therapy. *Supportive Care in Cancer* 2013;**21**(1):327-32.

Peterson 2015

Peterson D, Srivastava R, Lalla R. Oral mucosal injury in oncology patients: perspectives on maturation of a field. Oral Diseases 2015; Vol. 21, issue 2:133-41.

Scully 2006

Scully C, Sonis S, Diz PD. Oral mucositis. *Oral Diseases* 2006;**12**(3):229-41.

Sonis 2001

Sonis ST, Oster G, Fuchs H, Bellm L, Bradford WZ, Edelsberg J, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *Journal of Clinical Oncology* 2001;**19**(8):2201-5.

Sonis 2004

Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer* 2004;**100**(9 Suppl):1995-2025.

Sonis 2009

Sonis ST. Mucositis: The impact, biology and therapeutic opportunities of oral mucositis. *Oral Oncology* 2009;**45**(12):1015-20.

Trotti 2003

Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiotherapy and Oncology* 2003;**66**(3):253-62.

Wang 2015

Wang L, Gu Z, Zhai R, Zhao S, Luo L, Li D, et al. Efficacy of oral cryotherapy on oral mucositis prevention in patients with hematological malignancies undergoing hematopoietic stem cell transplantation: a meta-analysis of randomized controlled trials. *PLoS One* 2015;**10**(5):e0128763.

Williamson 2005

Williamson PR, Gamble C, Altman DG, Hutton JL. Outcome selection bias in meta-analysis. *Statistical Methods in Medical Research* 2005;**14**(5):515-24.

Williamson 2012

Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012;**13**:132.

Worthington 2015

Worthington H, Clarkson J, Weldon J. Priority oral health research identification for clinical decision-making. *Evidence-based Dentistry* 2015;**16**(3):69-71.

References to other published versions of this review

Riley 2015

Riley P, Glenny AM, Worthington HV, Littlewood A, Clarkson JE, McCabe MG. Interventions for preventing oral mucositis in patients with cancer receiving treatment: oral cryotherapy. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: 10.1002/14651858.CD011552]

Worthington 2011

Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, Littlewood A, et al. Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database of Systematic Reviews* 2011, Issue 4. [DOI: 10.1002/14651858.CD000978.pub5]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Askarifar 2015

Methods	**Trial design:** parallel (2 arms)
	Location: Iran
	Number of centres: 1
	Study duration: April to September 2013

Askarifar 2015 *(Continued)*

Participants	**Inclusion criteria:** full consciousness; suffering Hodgkin or non-Hodgkin lymphoma or multiple myeloma; good oral health; isolation in a separate room; undergoing similar basic chemotherapy; undergoing first course of chemotherapy; undergoing autologous BMT **Exclusion criteria:** patient dissatisfaction; loss of consciousness; susceptible to other diseases that could potentially disrupt treatment; use of analgesics continuously prior to start of study; receiving combined therapies such as radiotherapy; fever; neutropenia; mucositis prior to the treatment; respiratory diseases; oral infections; systemic diseases affecting oral health (especially periodontal tissues); more than 2 weeks interval between chemotherapy and transplantation; changes in treatment protocol during the study **Cancer type:** haematological (Hodgkin: Gp A: 31%; Gp B: 46%; non-Hodgkin: Gp A: 13%; Gp B: 23%; multiple myeloma: Gp A: 56%; Gp B: 31%) **Cancer treatment:** melphalan for Hodgkin and non-Hodgkin lymphoma; melphalan, cytarabine, etoposide, and lomustine for multiple myeloma ("There were no differences in terms of...treatment regimen") **Any other potentially important prognostic factors:** "There were no differences in terms of...educational status"; smokers: Gp A: 13%; Gp B: 31% **Age at baseline (years):** Gp A: 43 (range 19 to 66); Gp B: 39.8 (range 21 to 62) **Gender:** Gp A: 56% male; Gp B: 62% male **Number randomised:** 33 (Gp A: 17; Gp B: 16) **Number evaluated:** 29 (Gp A: 16; Gp B: 13)
Interventions	**Comparison: cryotherapy versus normal saline** **Gp A:** prior to BMT, ice cubes held in mouth 5 min before start of chemotherapy, held for 30-min periods with maximum 20-min breaks between each period, until 5 min after completion of chemotherapy **Gp B:** prior to BMT, 30 to 50 cc of saline mouthwash used 30 min before start of chemotherapy, then again every half-hour, until 6 hours after completion of chemotherapy **Compliance:** not reported **Duration of treatment (intended):** not reported but probably variable depending on chemotherapy regimen
Outcomes	• Oral mucositis: WHO 0 to 4 scale (assessed on days 3, 7, 14 and 21 and reported as a mean on each separate assessment day); we requested maximum score experienced per participant over the whole study period but the authors provided incidence of each grade on days 3, 7 and 14 • Neutrophil rate (not an outcome of this review)
Notes	**Sample size calculation:** based on detection of MD of 0.51, with 80% power at 5% significance level, and accounting for 40% attrition (14 per group required) **Adverse effects:** not reported **Funding:** "financial support of Tabriz University of Medical Sciences" **Declarations/conflicts of interest:** "Authors declare no conflict of interest in this study" **Data handling by review authors:** the authors provided us with data on the incidence of each oral mucositis grade on days 3, 7 and 14, and we used the data for day 7 in our meta-analyses as the incidence of grades > 0 was highest and therefore probably most closely equates to the maximum score experienced per participant (as reported in the other studies in the meta-analyses)

Askarifar 2015 *(Continued)*

	Other information of note: the information on this study is obtained from a pre-publication copy of the study report provided to us by the authors, and also from correspondence with the authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients randomly were allocated into control and intervention groups using size-2 random blocks and based on a 1:1 allocation ratio random numbers were generated by "Random software Allocation" software" Comment: computer generated randomisation so probably done adequately
Allocation concealment (selection bias)	Low risk	Quote: "The patients randomly were allocated into control and intervention groups using size-2 random blocks and based on a 1:1 allocation ratio random numbers were generated by "Random software Allocation" software" Correspondence: "the allocation was performed by a person who was not involved in sampling and analysis" Comment: appears to be third-party randomisation which should have ensured that the allocation sequence was not manipulated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel to allocated groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	The subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments
Incomplete outcome data (attrition bias) All outcomes	High risk	12% of randomised participants were not included in the analyses (Gp A: 6%; Gp B: 19%). All drop-outs were due to fever but this could be a risk of bias if the fever was linked to oral mucositis
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Cascinu 1994

Methods	**Trial design:** parallel (2 arms) **Location:** Pesaro, Italy **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** first ever course of chemotherapy **Exclusion criteria:** not reported **Cancer type:** Gp A: 98% gastrointestinal, 2% prostrate; Gp B: 98% gastrointestinal, 2% prostrate **Cancer treatment:** 5FU, different dosages and co-treatments (LV, IFN, VP16) equally distributed between groups due to stratification

Cascinu 1994 *(Continued)*

	Any other potentially important prognostic factors: performance status (EOCG): Gp A: 0 = 50%, 1 = 32%, 2 = 18%; Gp B: 0 = 50%, 1 = 35%, 2 = 15%; denture wearers equally distributed between groups due to stratification **Age at baseline (years):** Gp A: median 60 (range 38 to 73); Gp B: median 58 (range 44 to 72) **Gender:** Gp A: 68% male; Gp B: 70% male **Number randomised:** 84 (Gp A: 44; Gp B: 40) **Number evaluated:** 84 (Gp A: 44; Gp B: 40)
Interventions	**Comparison: cryotherapy versus no treatment** **Gp A:** ice chips placed in mouth 5 min before 5FU and continuously swished around, then replenished before the previous ice had completely melted, for total 30 min **Gp B:** 5FU only All participants were asked to remove dentures **Compliance:** all Gp A participants received cryotherapy in the first cycle but 2 participants "noted an 'ice cream' headache which caused them to refuse this technique after the second and third cycle of chemotherapy, respectively" **Duration of treatment (intended):** not reported (variable and dependent on number of cycles of cancer treatment)
Outcomes	• Oral mucositis: global assessment of the physician's judgement and participants' description on a 0 to 4 scale (very similar to WHO scale and NCI common toxicity criteria) based on methods of Mahood 1991 (assessed after each cycle and reported as first cycle only and all cycles, maximum score reported) • Duration of oral mucositis (not an outcome of this review) • Other adverse effects of cancer treatment (not an outcome of this review)
Notes	**Sample size calculation:** not reported **Adverse effects:** 2 participants in the cryotherapy group "noted an 'ice cream' headache" **Funding:** not reported **Declarations/conflicts of interest:** not reported **Data handling by review authors:** data reported as all cycles (so double-counting is a problem) and first cycle only, so we used the data for first cycle only **Other information of note:** mean oral mucositis score reported by smoking status for each group for the first cycle only (smokers had higher mean oral mucositis score than non-smokers in both groups)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised to a control arm or to receive cryotherapy" Correspondence: "Randomisation using cards from a computer generated list in sealed envelopes was performed by a person not involved with the care or evaluation of the patient" Comment: adequate method of random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "randomised to a control arm or to receive cryotherapy"

Cascinu 1994 *(Continued)*

		Correspondence: "Randomisation using cards from a computer generated list in sealed envelopes was performed by a person not involved with the care or evaluation of the patient" Comment: third-party randomisation and use of sealed envelopes should have ensured that the allocation sequence was not manipulated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel to allocated groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	The subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately. Although only the oral mucositis outcome was mentioned in the methods, this is more likely to be related to reporting quality rather than bias as the study pre-dates the CONSORT statement (CONSORT 2010)
Other bias	Low risk	No other sources of bias are apparent

Gori 2007

Methods	**Trial design:** parallel (2 arms) **Location:** various locations in Italy **Number of centres:** "multicentre" but unclear how many centres; co-ordinated by the Institute of Hematology and Medical Oncology, University of Bologna **Study duration:** October 2004 to January 2006
Participants	**Inclusion criteria:** undergoing allogeneic HSCT and MTX-containing GVHD prophylaxis; minimum age 8 years **Exclusion criteria:** clinical evidence of oral mucositis; participants not receiving at least 3 administrations of MTX following HSCT **Cancer type:** haematological (types were equally distributed between groups) **Cancer treatment:** pre-transplant radio/chemotherapy generally comparable between groups; total body irradiation: Gp A: 30.6%; Gp B: 28.3% **Any other potentially important prognostic factors:** stem cell donor related: Gp A: 45.1%; Gp B: 58.3%; stem cell source: Gp A: marrow = 33.9%, peripheral blood = 66.1%; Gp B: marrow = 28.3%, peripheral blood = 71.7%; folinic acid rescue: Gp A: 43.5%; Gp B: 38.3% **Age at baseline (years):** Gp A: median 35.5 (range 9 to 59); Gp B: median 40 (range 8 to 66) **Gender:** Gp A: 51.6% male; Gp B: 50% male **Number randomised:** 130 (not reported by group)

Gori 2007 *(Continued)*

	Number evaluated: 122 (Gp A: 62; Gp B: 60)
Interventions	**Comparison: cryotherapy versus no treatment** **Gp A:** after allogeneic HSCT, ice chips (mineral water) or popsicles placed in mouth for minimum 60 min starting from the time of low-dose MTX administration (20 mg/m^2 on day +1, 15 mg/m^2 on days +3, +6 and +11) as an IV infusion lasting 5 min (± 2), and replenished when melted **Gp B:** after allogeneic HSCT, MTX as above **Compliance:** "Six patients enrolled in the cryotherapy arm did not actually complete cryotherapy as planned because of refusal or poor tolerance. However, the exclusion of these patients did not change the results" **Duration of treatment (intended):** 4 occasions (minimum of 60 min) on 4 separate days (days 1, 3, 6 and 11)
Outcomes	• Oral mucositis: WHO 0 to 4 scale (assessed once daily for 20 to 30 days, maximum score reported) • Duration of moderate to severe (grade 2 to 4) and severe (grade 3 to 4) oral mucositis (not an outcome of this review)
Notes	**Sample size calculation:** based on previous study, 90% power at 5% significance (unclear whether required sample size was achieved) **Adverse effects:** not reported, only refers to the 6 participants who did not complete cryotherapy due to "refusal or poor tolerance" **Funding:** "We thank the Italian HSCT Nurses Group (GITMO) for sponsoring the study" **Declarations/conflicts of interest:** not reported **Data handling by review authors:** data is maximum oral mucositis score across all cycles of MTX **Other information of note:** univariate and multivariate analyses showed severe (grade 3 to 4) oral mucositis was significantly associated with total body irradiation and lack of folinic acid rescue

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After giving their informed consent, patients were included in a preformed randomization list that was updated by the coordinating center. Randomization was performed at the ratio of 1 patient per arm with no further stratifications" Comment: adequate method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "After giving their informed consent, patients were included in a preformed randomization list that was updated by the coordinating center. Randomization was performed at the ratio of 1 patient per arm with no further stratifications" Comment: co-ordinating centre mentioned, but unclear whether or not they allocated participants remotely from this centre (central randomisation by a third party)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel to allocated groups

Gori 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	The subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	6% of the participants were not included in the analyses but this attrition was not reported by group. However, the amount of attrition was low and reasons are fully reported
Selective reporting (reporting bias)	Low risk	Data for the primary outcome of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Heydari 2012

Methods	**Trial design:** parallel (2 arms) **Location:** Mashhad, Iran **Number of centres:** 2 **Study duration:** March 2007 to April 2008
Participants	**Inclusion criteria:** able to undergo one of the chemotherapy regimens described in the study at a standard dose; normal laboratory levels (including complete blood counts); normal kidney and hepatic function; participant or carer able to read and write **Exclusion criteria:** previous chemotherapy; not undergoing one of the combined courses of chemotherapy described in the study; treated with head and neck radiotherapy; diabetic **Cancer type:** Gp A: 55% colorectal, 45% breast; Gp B: 45% colorectal, 55% breast **Cancer treatment:** • MAYO (mean infusion time 20 min): 5FU (425 mg/m^2) and LV (25 mg/m^2) for 5 days, repeated every 28 days: Gp A: 55%; Gp B: 45% • CAF (mean infusion time 25 to 35 min): cyclophosphamide (500 mg/m^2), adriamycin (50 mg/m^2) and 5FU (500 mg/m^2) on 1st day of cycle, repeated every 21 days: Gp A: 30%; Gp B: 42.5% • CMF (mean infusion time 25 to 35 min): cyclophosphamide (600 mg/m^2), MTX (40 mg/m^2) and 5FU (600 mg/m^2) on 1st day of cycle, repeated every 28 days: Gp A: 15%; Gp B: 12.5% **Any other potentially important prognostic factors:** no statistically significant differences between groups in the following factors: tooth status, smoking status, mouthwash use, brushing habit, BMI, educational status **Age at baseline (years):** Gp A: mean 59.5 (SD 12.35); Gp B: mean 63.25 (SD 15.06) **Gender:** 40% male overall and reports that there were no statistically significant differences between groups **Number randomised:** 80 (Gp A: 40; Gp B: 40) **Number evaluated:** 80 (Gp A: 40; Gp B: 40)
Interventions	**Comparison: cryotherapy versus no treatment** **Gp A:** ice chips placed in mouth 5 min before chemotherapy until 5 min after and continuously swished around, then replenished before the previous ice had completely melted

Heydari 2012 *(Continued)*

	Gp B: chemotherapy only All participants were asked to remove dentures **Compliance:** well tolerated, no discontinuation of therapy, and most participants kept their mouths constantly cool for most of the chemotherapy session **Duration of treatment (intended):** mean duration of cryotherapy was 20 to 45 min for a session; those receiving MAYO regimen (*see* above) had cryotherapy for each of the 5 days of treatment, whilst those receiving CAF/CMF regimen (*see* above) had cryotherapy on the single day of treatment
Outcomes	• Oral mucositis: WHO 0 to 4 scale assessed separately by participants and clinicians (first cycle-only reported, assessed daily by participants or on days 1, 5, 14 and 21 for the 5-day regimen (MAYO) and days 7, 14 and 21 for the single-day regimens (CAF/CMF), maximum score reported) **Obtained from correspondence:** • Interruptions to cancer treatment: (assessed over first 2 cycles, reported as both event (dichotomous) data and continuous data in the form of mean number of days of interruption) • Oral pain: 1 to 5 scale relating to duration of pain experience (1 = never, 2 = one day of week, 3 = 2 to 3 days of week, 4 = most of week, 5 = 7 days of week)
Notes	**Sample size calculation:** not reported **Adverse effects:** 8 (20%) of participants in the cryotherapy group complained of chills **Funding:** "This work was supported by the department of research, Mashhad University of Medical Science" **Declarations/conflicts of interest:** not reported **Data handling by review authors:** clinician judgement of oral mucositis was preferred over participant judgement as we deemed that this may be more objective and less biased; oral pain was measured in a different way to the other studies measuring intensity/severity of pain and therefore it is not appropriate to meta-analyse using standardised mean difference, so we have presented the data in an additional table **Other information of note:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by the use of a random numbers table" Comment: adequate method of random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by the use of a random numbers table" Correspondence: "We designed a list that numbered from 100 to 180. Then an external person involved assigning a letter (A, AB, B, and BA) to the each number randomly. The entire investigator was blinded about number and letters. As patients enrolled for study, the external person enters the patient's code in the list. In summary, we used an external person to allocate patient to the intervention or control group" Comment: third-party randomisation should have ensured that the allocation sequence was not manipulated
Blinding of participants and personnel (performance bias)	High risk	Not possible to blind participants and personnel to allocated groups

Heydari 2012 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	The subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Kakoei 2013

Methods	**Trial design:** parallel (2 arms) **Location:** Kerman, Iran **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** partial or complete exposure of head and neck to radiation; minimum radiation dose of 2500 to 3000 cGy (trial registry says Gy) per session; beginning radiotherapy at the start of the study and continuing constantly for the following 2 weeks **Exclusion criteria:** existing oral mucositis; systemic disease or medication affecting oral condition; less than 15 or more than 55 years of age **Cancer type:** head and neck (not reported by group) **Cancer treatment:** radiotherapy to the head and neck **Any other potentially important prognostic factors:** no statistically significant difference between groups in smoking status or education level **Age at baseline (years):** Gp A: mean 42.9 (SD 14.9); Gp B: mean 49.1 (SD 15.4) **Gender:** 57.5% male overall and reports that there were no statistically significant differences between groups **Number randomised:** 40 (Gp A: 20; Gp B: 20) **Number evaluated:** 40 (Gp A: 20; Gp B: 20)
Interventions	**Comparison: cryotherapy versus no treatment** **Gp A:** ice cubes placed in mouth and sucked for 5 min before radiotherapy and for a further 5 min after the session **Gp B:** standard oral care Both groups received standard oral care (use of soft toothbrush, nonabrasive toothpaste and dental floss twice daily) **Compliance:** only states "no lapse during the study"

Kakoei 2013 *(Continued)*

	Duration of treatment (intended): 10 min per day for 2 weeks
Outcomes	• Oral mucositis: 0 to 4 scale assessed separately by participants and clinicians (very similar to WHO scale and NCI common toxicity criteria - based on methods of Mahood 1991) (assessed on days 1, 7 and 14 and reported as a mean on each separate assessment day) • Oral pain: scale not mentioned (assessed days 1, 7 and 14 and reported as a mean on each separate assessment day)
Notes	**Sample size calculation:** 80% power at 5% significance level to detect a 40% difference in treatment effect (as there were no drop-outs, it is assumed that this was achieved) **Adverse effects:** not reported but presumably none were expected due to the 5-min periods of cryotherapy **Funding:** "This study was financially supported by the Office of Vice Chancellor for Research of Kerman University of Medical Sciences" **Declarations/conflicts of interest:** not reported **Data handling by review authors:** we report MD and 95% CI for mucositis severity in an additional table; physician-judged mucositis rating was preferred over participant judgement as we deemed that this may be more objective and less biased; we used the data on day 14 due to the highest control group mean; we were unable to use the oral pain data as the scale was not described **Other information of note:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The participants were divided into experimental and control groups using block randomization technique with the formula of AABB, ABAB, ABBA, BBAA, BABA, and BAAB" Comment: random sequence appears to have been adequately generated
Allocation concealment (selection bias)	Unclear risk	Quote: "The participants were divided into experimental and control groups using block randomization technique with the formula of AABB, ABAB, ABBA, BBAA, BABA, and BAAB" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel to allocated groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	The subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	High risk	Oral pain not mentioned in the trial registry record and not described in the methods of the published trial report. It is possible that this was reported because it showed favourable results for cryotherapy

Kakoei 2013 *(Continued)*

Other bias	Low risk	No other sources of bias are apparent

Katranci 2012

Methods	**Trial design:** parallel (2 arms) **Location:** Gaziantep, Turkey **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** due to receive first course of chemotherapy; healthy oral mucosa; no dental problems **Exclusion criteria:** receiving more than 1 combination chemotherapy course or antineoplastic drug treatment with half-life of 30 min or more; discomfort in the mouth; head-neck cancer **Cancer type:** gastric 33.3%; colon 33.3%; rectal 16.9%; pancreatic 9.9%; unknown 6.6% (equal numbers per group); stage of disease equally distributed between groups **Cancer treatment:** 5FU and LV **Any other potentially important prognostic factors:** education level, denture wearers, toothbrushing habits, smoking status, nutrition, dry mouth, lack of appetite and systemic disease all equally distributed between groups **Age at baseline (years):** not reported **Gender:** 50% male in both groups **Number randomised:** 60 (Gp A: 30; Gp B: 30) **Number evaluated:** 60 (Gp A: 30; Gp B: 30)
Interventions	**Comparison: cryotherapy versus routine care** **Gp A:** ice chips placed in mouth 5 min before 5FU + LV, during treatment and within 15 min after treatment, for total 30 min; continuously swished around, then replenished before the previous ice had completely melted; whole procedure repeated for 5 consecutive days **Gp B:** routine care All participants were asked to remove dentures **Compliance:** "Oral cryotherapy was tolerated well by the patients. The majority of the patients reported that they managed to keep the oral cavity constantly cooled most of the time that the chemotherapy treatment was administered. Patients who experienced discomfort during the cryotherapy application continued their treatment after a maximum 30-60 s break" **Duration of treatment (intended):** 30 min per day for 5 days (first cycle only)
Outcomes	• Oral mucositis: WHO 0 to 4 scale (assessed and reported on days 7, 14 and 21 - i.e. not reported as maximum score per participant)
Notes	**Sample size calculation:** not reported **Adverse effects:** "The patients completed the procedure quite comfortably, without any problems during the application" **Funding:** not reported

Katranci 2012 *(Continued)*

Declarations/conflicts of interest: "None declared"

Data handling by review authors: data were reported separately on the 3 assessment days rather than a maximum score per person over the whole assessment period. We used the data on the day with the highest incidence of grades > 0 (day 14), although we are not sure how valid this is because there was still a high incidence of severe oral mucositis at day 21

Other information of note: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed by MedCalc software to give equal chance to assign each intervention group" Comment: computer generated randomisation so probably done adequately
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomisation was performed by MedCalc software to give equal chance to assign each intervention group" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel to allocated groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	The subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Lilleby 2006

Methods	**Trial design:** parallel (2 arms) **Location:** Seattle, USA **Number of centres:** 1 **Study duration:** August 2003 to June 2005
Participants	**Inclusion criteria:** minimum age 18 years with multiple myeloma; scheduled to receive single-agent high-dose melphalan (200 mg/m^2) followed by autologous PBSCT 2 days later **Exclusion criteria:** previous autologous PBSCT **Cancer type:** haematological (multiple myeloma)

Lilleby 2006 *(Continued)*

	Cancer treatment: high-dose melphalan (200 mg/m^2) followed by autologous PBSCT **Any other potentially important prognostic factors:** not reported **Age at baseline (years):** Gp A: median 59 (range 51 to 71); Gp B: median 57 (range 33 to 72) **Gender:** Gp A: 76.2% male; Gp B: 63.2% male **Number randomised:** 41 (Gp A: 21; Gp B: 20) **Number evaluated:** 40 (Gp A: 21; Gp B: 19) (above figures for age and gender are for evaluated participants)
Interventions	**Comparison: cryotherapy versus saline rinse** **Gp A:** 2 days before stem cell infusion, 1 ounce of ice chips held in mouth 30 min prior to beginning single-agent high-dose melphalan (200 mg/m^2) infusion, replenished when melted, procedure continued for 6 hours after the end of the 30-min melphalan infusion **Gp B:** 2 days before stem cell infusion, 1 ounce of room temperature normal saline swished around the mouth and spat out 30 min prior to beginning single-agent high-dose melphalan (200 mg/m^2) infusion, procedure repeated every 30 min for 6 hours after the end of the 30-min melphalan infusion All participants instructed not to eat or drink anything extremely hot or cold during cryotherapy/saline treatment **Compliance:** 14 participants had at least 5 hours of cryotherapy, and 2 had at least 2 hours, whilst 5 did not report the duration. Some participants stopped using the ice chips due to their coldness. Average frequency of use: cryotherapy: 1 cup/hour; saline: 1 to 4 rinses/hour **Duration of treatment (intended):** 7 hours
Outcomes	• Oral mucositis: NCI-CTC 0 to 4 scale (assessed until 30 days after cryotherapy/saline administration, maximum score reported) • Normalcy of diet: duration of TPN (assessed until 30 days after cryotherapy/saline administration) • Duration of IV narcotic use (assessed until 30 days after cryotherapy/saline administration) • Duration of hospitalisation (assessed until 30 days after cryotherapy/saline administration) • Weight loss (not an outcome of this review) • First day 30% of calorific needs met (not an outcome of this review) Patient-reported events: • Mouth and throat pain: 0 to 10 scale (assessed daily by questionnaire until 30 days after cryotherapy/saline administration) • Adverse effects of cancer treatment: difficulties swallowing, drinking, eating, talking, sleeping and taste disturbance (not outcomes of this review)
Notes	**Sample size calculation:** required sample size was achieved ("sample size of 40 was chosen to provide 91% power to observe a statistically significant difference (at the 2-sided significance level of 0.05) in the probability of grades 3–4 mucositis under the assumption that the true probabilities of severe mucositis are 0.25 for patients receiving ice chips and 0.75 for patients receiving normal saline") **Adverse effects:** not reported, only refers to some participants that stopped using the ice chips due to their coldness **Funding:** "This work was supported by Friends of Jose Carreras International Leukemia Foundation Presidential Award, NCI P01 CA-18029" **Declarations/conflicts of interest:** not reported **Data handling by review authors:** for patient-reported oral pain, we used the mean, number of participants and P value to calculate a single SD to be used for both groups (we used the overall mean

Lilleby 2006 *(Continued)*

	pain scores rather than the number of days of pain or the mean of the highest value); only medians and ranges presented for the outcomes days of TPN, IV narcotics and hospitalisation, so we present the results, as reported in the study report, in an additional table
	Other information of note: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients...were randomized to receive either ice chips or room temperature normal saline rinses" Correspondence: "randomisation was accomplished using a computer program designed by one of our statisticians" Comment: adequate method of random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "patients...were randomized to receive either ice chips or room temperature normal saline rinses" Correspondence: "Central randomization from the protocol office" Comment: central randomisation should have ensured that the allocation sequence was not manipulated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel to allocated groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	The subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 randomised participant, from the control group, was not included in the analyses. The participant withdrew consent because he wanted to use ice chips
Selective reporting (reporting bias)	Low risk	Although the data for some outcomes of this review were not presented in a way amenable to meta-analysis, this is unlikely to be due to bias
Other bias	Low risk	No other sources of bias are apparent

Mahood 1991

Methods	**Trial design:** cross-over (2 arms) **Location:** USA **Number of centres:** unclear (multicentre) **Study duration:** not reported
Participants	**Inclusion criteria:** first ever course of chemotherapy **Exclusion criteria:** not reported **Cancer type:** not reported but must be solid due to chemotherapy regimen

Mahood 1991 *(Continued)*

	Cancer treatment: 5FU and LV **Any other potentially important prognostic factors:** not reported **Age at baseline (years):** not reported **Gender:** not reported **Number randomised:** 95 (Gp A: 50; Gp B: 45) **Number evaluated:** 93 (Gp A: 50; Gp B: 43)
Interventions	**Comparison: cryotherapy versus no treatment** **Gp A:** ice chips placed in mouth 5 min before receiving 5FU (425 mg/m^2) and LV (20 mg/m^2) by IV over a few minutes, and continuously swished around, then replenished before the previous ice had completely melted, for total 30 min, whole procedure repeated for 5 consecutive days **Gp B:** 5FU (425 mg/m^2) and LV (20 mg/m^2) only for 5 consecutive days All participants were asked to remove dentures **Compliance:** not clearly reported. Only states "well tolerated by most patients" **Duration of treatment (intended):** 30 min per day for 5 days (first cycle only)
Outcomes	• Oral mucositis: physician judgement and participant judgement both on a 0 to 4 scale (very similar to WHO scale and NCI common toxicity criteria) (physician's judgement assessed by historical means approximately 1 month after treatment initiation, maximum score reported) • Duration of oral mucositis (not an outcome of this review)
Notes	**Sample size calculation:** not reported **Adverse effects:** "A few patients noted mild, temporary mouth numbness or an "ice cream" headache which rapidly resolved after cessation of cryotherapy. Also, some patients ascribed nausea to the oral ice chips (the nausea may have actually been from the 5FU)" **Funding:** "supported in part by Public Health Service grants...and Community Clinical Oncology Program grants" **Declarations/conflicts of interest:** not reported **Data handling by review authors:** we only used the data from the first treatment cycle (rather than cross-over data); physician judgement of oral mucositis was preferred over participant judgement as we deemed that this may be more objective and less biased **Other information of note:** mean oral mucositis score reported by smoking status for each group for the first cycle only (smokers had statistically significantly lower mean oral mucositis score than non-smokers, but data not available for all participants)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Prior to therapy, patients were stratified by age and whether or not they had dentures. They were then randomized to a control arm or to receive cryotherapy" Comment: insufficient information to determine method of random sequence generation

Mahood 1991 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "Prior to therapy, patients were stratified by age and whether or not they had dentures. They were then randomized to a control arm or to receive cryotherapy" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel to allocated groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	The subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 randomised participants, both from the control group, were not included in the physician-judged oral mucositis analyses. We do not believe that this could pose a risk of bias significant enough to have led to a distortion of the true intervention effect
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Rocke 1993

Methods	**Trial design:** cross-over (2 arms) **Location:** USA **Number of centres:** unclear (multicentre) **Study duration:** not reported
Participants	**Inclusion criteria:** first course of chemotherapy **Exclusion criteria:** not reported **Cancer type:** not reported but must be solid due to chemotherapy regimen **Cancer treatment:** 5FU and LV, different dosages taken orally or by IV, equally distributed between groups due to stratification **Any other potentially important prognostic factors:** participants were stratified by smoking status, dentures and institution/centre; gum condition not used for stratification but Gp B (60 min cryotherapy) had worse gums at baseline (P = 0.02) **Age at baseline (years):** Gp A: median 65 (range 24 to 79); Gp B: median 65 (range 25 to 85) **Gender:** Gp A: 55% male; Gp B: 51% male **Number randomised:** 179 (Gp A: 90; Gp B: 89) **Number evaluated:** 178 (Gp A: 89; Gp B: 89)
Interventions	**Comparison: 30 min of cryotherapy versus 60 min of cryotherapy**

Rocke 1993 *(Continued)*

	Gp A: ice chips placed in mouth 5 min before receiving 5FU and LV, and continuously swished around, then replenished before the previous ice had completely melted, for total 30 min, whole procedure repeated for 5 consecutive days **Gp B:** as above but for total 60 min All participants were asked to remove dentures **Compliance:** well tolerated with high degree of compliance. Only a few participants stopped cryotherapy early (due to nausea, headache or chills). Many participants in the 60-min group were unhappy with the duration of cryotherapy, indicating that 30 min of cryotherapy is preferred **Duration of treatment (intended):** 30 or 60 min per day for 5 days (first cycle only)
Outcomes	• Oral mucositis: physician judgement and participant judgement both on a 0 to 4 scale (very similar to WHO scale and NCI common toxicity criteria) (physician's judgement assessed by historical means approximately 1 month after treatment initiation, maximum score reported) • Duration of oral mucositis (not an outcome of this review)
Notes	**Sample size calculation:** not reported **Adverse effects:** only a few participants stopped cryotherapy early (due to nausea, headache or chills) **Funding:** "supported in part by Public Health Service grants...from the National Cancer Institute, Department of Health and Human Services" **Declarations/conflicts of interest:** not reported **Data handling by review authors:** we only used the data from the first treatment cycle (rather than cross-over data); physician judgement of oral mucositis was preferred over participant judgement as we deemed that this may be more objective and less biased **Other information of note:** in exploratory analyses, age over 65 years was statistically significantly ($P < 0.001$) associated with severity of mucositis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized to receive cryotherapy for either 30 or 60 minutes" Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomized to receive cryotherapy for either 30 or 60 minutes" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel to allocated groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	The subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments

Rocke 1993 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 randomised participant, from the cryotherapy group, was not included in the analyses due to an unrelated medical problem
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Salvador 2012

Methods	**Trial design:** parallel (2 arms) **Location:** Toronto, Canada **Number of centres:** 1 **Study duration:** May to December 2007
Participants	**Inclusion criteria:** minimum 18 years of age; able to read and understand instructions on oral cryotherapy and basic oral care in English; diagnosis of multiple myeloma; due to receive high-dose melphalan (200 mg/m^2); due to receive growth factors as part of treatment protocol; no pre-existing oral disease **Exclusion criteria:** previous radiotherapy to the head and neck region; amyloidosis (when abnormal proteins collect together and build up in tissues/organs) involving the heart, kidneys, or tongue; receiving investigational drugs during the trial period **Cancer type:** haematological (multiple myeloma) **Cancer treatment:** high-dose melphalan (200 mg/m^2) followed by autologous SCT **Any other potentially important prognostic factors:** college/university educated: Gp A: 43%; Gp B: 16%; smokers: Gp A: 17%; Gp B: 9%; drinks alcohol: Gp A: 35%; Gp B: 27% **Age at baseline (years):** Gp A: mean 56 (SD 8.9) (range 43 to 72); Gp B: mean 62 (SD 7.7) (range 43 to 72) **Gender:** Gp A: 61% male; Gp B: 55% male **Number randomised:** 46 (Gp A: 23; Gp B: 23) **Number evaluated:** 45 (Gp A: 23; Gp B: 22)
Interventions	**Comparison: cryotherapy versus no treatment** **Gp A:** on day -1 (the day before autologous SCT), ice chips held in mouth 5 min prior to receiving high-dose melphalan (200 mg/m^2), replenished before melted, procedure continued until 5 min after melphalan infusion, for total 60 min. Basic oral care also received (described below) from day -1 **Gp B:** on day -1, basic oral care began (described below) All participants received high-dose melphalan on day -1 and SCT the following day (day 0). On average, participants stayed in hospital for 14 days after SCT. During the engraftment period, patients also received similar treatment and care protocols: prophylactic antimicrobial, antiviral and antacid (day 1), and growth factor (granulocyte colony-stimulating factor) (day 7); and basic oral care protocol (day -1). Oral care protocol consisted of regular oral assessment and documentation, patient education on OM, and training in oral self care (toothbrushing with Toothette sponges dipped in sodium bicarbonate mouthwash, mouthrinsing with sodium bicarbonate mouthwash, and application of moisturiser to lips and oral cavity).

Salvador 2012 *(Continued)*

	Compliance: all participants were able to perform the basic oral care procedures and all participants in the cryotherapy group complied with the intervention **Duration of treatment (intended):** basic oral care from day -1 to day 12 (14 days); oral cryotherapy for 60 min on day -1
Outcomes	• Oral mucositis: WHO 0 to 4 scale (assessed on days 3, 6, 9 and 12 and reported as a mean on each separate assessment day - not reported for day 3 as OM had not yet developed); we requested maximum score experienced per participant over the whole study period and the author provided this data • Oral pain: 0 to 10 VAS (assessed on days 3, 6, 9 and 12 and reported as an overall mean score) • Duration of hospital stay (mean number of days, measured as total number of days from admission to discharge - all participants were treated as inpatients) • Normalcy of diet: functional intake of food and fluids on 1 (solids) to 5 (nothing by mouth) scale (assessed on days 3, 6, 9 and 12 and reported in a mixed-effects regression analysis) • Time to onset, duration and time to resolution of oral mucositis (not an outcome of this review) • Amount of opioid analgesics used (not an outcome of this review)
Notes	**Sample size calculation:** 17 participants per group needed to detect an effect size of 1 (presumably the authors mean a MD of 1 on the WHO scale) at 80% power and 5% significance **Adverse effects:** 4 participants (17.4%) in the cryotherapy group experienced side effects (teeth sensitivity and chills) **Funding:** "The authors acknowledge the financial support of the University Health Network Nursing Research and Canadian Nurses Foundation for the successful implementation of the project" **Declarations/conflicts of interest:** "The authors have nothing to disclose and declare no conflicts of interest" **Data handling by review authors:** the authors provided the maximum score experienced per participant over the whole study period; we were unable to use the data on normalcy of diet **Other information of note:** although the authors report that the MD of 0.71 in OM severity (at day 9) was statistically significant, they state that it is not clinically significant because most participants only had OM grades of 0 to 1; conversely, the authors report that the difference in days of hospital stay was not statistically significant, but that the difference of approximately 1 day is clinically significant; we note an error in Table 2 where the mean in the control group at day 6 should be 0.5 rather than 0.05

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were allocated based on a randomization process performed by the biostatistics staff at the study site, using consecutively numbered sealed envelopes containing a computer-generated random number list patient assignment" Comment: adequate method of random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "Participants were allocated based on a randomization process performed by the biostatistics staff at the study site, using consecutively numbered sealed envelopes containing a computer-generated random number list patient assignment" Comment: these methods should have ensured that the allocation sequence was not manipulated
Blinding of participants and personnel (performance bias)	High risk	Not possible to blind participants and personnel to allocated groups

Salvador 2012 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Although described as blinded, the subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 randomised participant, from the control group, was not included in the analyses due to an adverse event related to the melphalan on the day of its administration
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Sorensen 2008

Methods	**Trial design:** parallel (3 arms) **Location:** Denmark **Number of centres:** unclear (appears to be multicentre) **Study duration:** 2001 to 2005
Participants	**Inclusion criteria:** gastric or colorectal cancers; due to receive first course of chemotherapy; healthy oral mucosa **Exclusion criteria:** history of head and neck radiotherapy; symptoms of any infections; history of dental or mouth discomfort when consuming hot/cold food and drinks **Cancer type:** approximately 95% colorectal cancer in each group, with the remainder having gastric cancer **Cancer treatment:** 5FU and LV **Any other potentially important prognostic factors:** participants were stratified by age, smoking status and dentures; performance status score was equally distributed between groups **Age at baseline (years):** Gp A: 40 or older = 97%, median 62 (range 36 to 84); Gp B: 40 or older = 95%, median 61 (range 30 to 81); Gp C: 40 or older = 92%, median 62 (range 28 to 82) **Gender:** Gp A: 60% male; Gp B: 53% male; Gp C: 53% male **Number randomised:** 225 (Gp A: 75; Gp B: 75; Gp C: 75) **Number evaluated:** reported in the study: 206 (Gp A: 67; Gp B: 66; Gp C: 73); data available for OM incidence: 197 (Gp A: 63; Gp B: 64; Gp C: 70)
Interventions	**Comparison: cryotherapy versus saline rinse (placebo version of chlorhexidine) versus chlorhexidine rinse** **Gp A:** crushed ice placed in mouth 10 min before receiving 5FU (425 mg/m^2) and LV (20 mg/m^2) by IV, and for 35 min after the start of infusion (total 45 min), whole procedure repeated for 5 consecutive days every 4 weeks **Gp B:** same cancer treatment but saline mouthwash (with same taste additives as Gp C), 10 ml swished around the mouth for 1 min, 3 times per day for 21 days **Gp C:** same cancer treatment but chlorhexidine 0.1% mouthwash, same schedule as Gp B

Sorensen 2008 *(Continued)*

	All participants were asked to remove dentures; participants were "instructed to continue prophylaxis in case OM occurred, which was treated according to the discretion of the respective investigators" **Compliance:** (complete) Gp A: 87%; Gp B: 80%; Gp C: 75%; (partial) Gp A: 13%; Gp B: 20%; Gp C: 25% **Duration of treatment (intended):** 45 min per day for 5 days per chemotherapy cycle (cryotherapy); 3 min per day for 21 days per chemotherapy cycle (chlorhexidine and saline rinses)
Outcomes	• Oral mucositis: NCI-CTC (2.0) 0 to 4 scale (first cycle-only reported at day 28, participants kept daily record and self-evaluated OM by questionnaire on days 14 and 28, physician also scored OM on days 14 and 28, participant score was reported as there were no statistically significant differences between participant and physician scores, maximum score reported) • Duration of oral mucositis (not an outcome of this review) • Compliance (not an outcome of this review) • Haematologic toxicity (not an outcome of this review)
Notes	**Sample size calculation:** considering a 15% decrease in incidence of grade 3 to 4 OM as being clinically meaningful, with 80% power and at the 5% significance level, 75 patients required per group. Therefore, considering drop-outs, required sample size was not achieved **Adverse effects:** taste disturbance: Gp A: 24/67 (36%); Gp B: 25/66 (38%); Gp C: 35/73 (48%); headache: Gp A: 14/67 (21%); Gp B: 9/66 (14%); Gp C: 10/73 (14%) **Funding:** "Supported by a grant from the National University Hospitals Research Foundation in Denmark" **Declarations/conflicts of interest:** not reported **Data handling by review authors:** the study authors report that data were available on 206 participants, however, for OM incidence, some of this number of participants are not given a grade and are listed as 'NA' (abbreviation not explained). We subtracted the 'NA' participants from the total number of participants and have addressed this problem under 'Incomplete outcome data (attrition bias)' **Other information of note:** smoking status, performance status and being aged 40 or older (underpowered - only 11 participants less than 40) were not statistically significantly associated with severity of OM

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were stratified...and randomized after informed consent to 1 of 3 prophylactic regimens" Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were stratified...and randomized after informed consent to 1 of 3 prophylactic regimens" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel to allocated groups
Blinding of outcome assessment (detection bias)	High risk	The subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments

Sorensen 2008 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	For OM incidence, 12% of randomised participants were not included in the analysis (Gp A: 16%; Gp B: 15%; Gp C: 9%). Reasons are not reported but there is a potential risk of bias if this differential drop-out is related to outcomes/prognosis
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Svanberg 2007

Methods	**Trial design:** parallel (2 arms) **Location:** Uppsala, Sweden **Number of centres:** 1 **Study duration:** January 2002 to August 2004
Participants	**Inclusion criteria:** more than 18 years of age; able to communicate in Swedish; about to receive BMT **Exclusion criteria:** not reported **Cancer type:** 1 participant per group had testicular cancer, the remainder had haematological cancers **Cancer treatment:** type of chemotherapy prior to BMT was fairly equally distributed between groups; participants were stratified by autologous BMT (both groups 79.5%) versus allogeneic URD BMT (both groups 20.5%) **Any other potentially important prognostic factors:** tobacco use equally distributed between groups (Gp A: 17.9%; Gp B: 15.4%) **Age at baseline (years):** Gp A: mean 49.8 (SD 14.4); Gp B: mean 54.3 (SD 11) **Gender:** Gp A: 66.7% male; Gp B: 48.7% male **Number randomised:** 78 (Gp A: 39; Gp B: 39) **Number evaluated:** 78 (Gp A: 39; Gp B: 39)
Interventions	**Comparison: cryotherapy versus no treatment** **Gp A:** prior to BMT (unclear how far in advance); ice chips placed in mouth or rinsing with ice-cold water starting 5 min before receiving chemotherapy by IV, and replenished for the duration of the chemotherapy session **Gp B:** chemotherapy prior to BMT All participants received standard oral care during BMT **Compliance:** 58% to 75% of the participants reported that they kept the mouth constantly cooled for the entire duration of the chemotherapy; 71% to 100% did so more than half the time **Duration of treatment:** not reported (variable and dependent on type of chemotherapy)
Outcomes	• Oral mucositis: OMAS (*see*Appendix 8 for details of scale) (assessed once daily for 21 days after start of chemotherapy by nurse, mean score reported on each day, reported separately for autologous/allogeneic BMT but no overall score reported)

Svanberg 2007 *(Continued)*

- Oral mucositis: WHO 0 to 4 scale (incidence of severe mucositis i.e. grade 3 to 4, assessed once daily for 21 days after start of chemotherapy) (outcome reported in secondary publication); we requested maximum score experienced per participant over the whole study period and the author provided this data
- Oral pain: 0 to 10 VAS (assessed twice daily (morning and afternoon) for 21 days after start of chemotherapy, reported verbally to nurse)
- Duration of opioid use (mean number of days, assessed over period of 31 days after start of chemotherapy from medical records)
- Duration of hospital stay (outcome reported in secondary publication) (mean number of days, assessed over period of 31 days after start of chemotherapy)
- Normalcy of diet: incidence of TPN and duration of TPN (outcome reported in secondary publication) (we used mean number of days, assessed over period of 31 days after start of chemotherapy)
- Weight loss (not an outcome of this review)
- Duration of fever (not an outcome of this review)
- Antibiotic use (not an outcome of this review)
- Total dose of opioids (not an outcome of this review)
- White blood cell counts and c-reactive protein levels (not outcomes of this review)

Notes

Sample size calculation: 36 participants per group needed for 80% power at 5% significance level (based on outcome 'duration of IV opioids')

Adverse effects: 7 (18%) of participants found cryotherapy unpleasant, with 4 of those (10%) finding it very unpleasant due to shooting pain from the teeth

Funding: "This study was in part supported by FoU funds, Uppsala läns landsting, Sweden"

Declarations/conflicts of interest: not reported

Data handling by review authors: we were unable to use the OMAS score but the authors provided full data for oral mucositis on the WHO scale; oral pain was not reported adequately so we were unable to report on this outcome

Other information of note: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A random assignment to EXP or CTR group was performed in blocks of six outside of the clinic by an independent researcher" Comment: if using block-randomisation, it could be assumed that the independent researcher would have done this adequately
Allocation concealment (selection bias)	Low risk	Quote: "A random assignment to EXP or CTR group was performed in blocks of six outside of the clinic by an independent researcher" Comment: third-party randomisation should have ensured that the allocation sequence was not manipulated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel to allocated groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	The subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments

Svanberg 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	High risk	Oral mucositis using OMAS and oral pain inadequately reported. Data are presented in the text for mucositis scores on day 10 (autologous patients) and day 16 (allogeneic patients), and this appears to be based on statistical significance. The study authors have since provided full data on the WHO scale. Therefore, our rating for this domain is based on the fact that the text only states that there was no significant differences for oral pain
Other bias	Low risk	45 staff members assessed mucositis using the OMAS instrument. Calibration is not mentioned. However, we were unable to use any data for this outcome so we can discount any potential bias

Toro 2013

Methods	**Trial design:** parallel (3 arms) **Location:** San Antonio, Texas, USA **Number of centres:** 1 **Study duration:** first subject randomised August 2009; last subject randomised January 2013
Participants	**Inclusion criteria:** minimum 18 years of age; diagnosis of multiple myeloma and scheduled to receive high-dose melphalan (70 to 100 mg/m^2/day) for 2 days, as a single agent, for conditioning regimen prior to HSCT **Exclusion criteria:** received palifermin (Kepivance) in the past 30 days; received any investigational drug in the past 30 days; received radiation therapy in the past 30 days; oral mucositis at the time of randomisation; altered mental status precluding understanding of the informed consent process and/or completion of the necessary assessments **Cancer type:** haematological (multiple myeloma) **Cancer treatment:** high-dose melphalan, prior to autologous HSCT **Any other potentially important prognostic factors:** no differences between groups in race/ethnicity, Karnofsky performance score, diabetes, denture wearing, smoking status **Age at baseline (years):** Gp A: median 62 (range 39 to 75); Gp B: median 61.5 (range 43 to 70) **Gender:** both groups 95% male **Number randomised:** 78 (Gp A: 40; Gp B: 38) (numbers are for the 2 groups of interest to this review) **Number evaluated:** 78 (Gp A: 40; Gp B: 38)
Interventions	**Comparison: cryotherapy plus saline rinse versus saline rinse** The 3rd group involved using supersaturated calcium phosphate rinse (Caphosol®) but we have excluded this arm because the co-intervention of cryotherapy plus saline may confound the comparison. The comparison of this 3rd group with the saline group will be included in our review of basic oral care interventions for the prevention of oral mucositis in cancer patients **Gp A:** on day -2 and -1 (HSCT was on day 0), approximately 1 ounce of crushed ice held in the mouth 15 min prior to the initiation of melphalan infusion, replenished as soon as it had completely melted, this procedure continued during the melphalan infusion and for 90 min after the end of the infusion. After completion of cryotherapy, standard care was followed until the end of the study (*see* Gp B below)

Toro 2013 *(Continued)*

	Gp B: standard care (0.9% sodium chloride irrigation solution): rinsing of mouth twice, with 1 ounce (30 ml) of room temperature 0.9% NaCl (normal saline), 4 times daily after admission and until end of study **Compliance:** 100% compliance with cryotherapy but 3 subjects from the saline group refused to follow protocol but were kept in study **Duration of treatment (intended):** 2 consecutive days (exact duration of cryotherapy sessions unclear)
Outcomes	• Oral mucositis: WHO 0 to 4 scale (assessed daily until resolution or hospital discharge up to a maximum of 30 days, maximum score reported) • Oral pain: scale not reported • Narcotic use: unclear whether or not reported as duration of opioid use or amount of opioid use • Quality of life: Patient-Reported Oral Mucositis Symptom (PROMS) scale (assessed daily until resolution of oral mucositis) • Duration of oral mucositis (not an outcome of this review)
Notes	**Sample size calculation:** "This study will achieve a power of 80% to detect a 0.30 reduction in the proportion of subjects experiencing mucositis relative to saline with 55 subjects per arm and relative to Caphosol with 43 subjects per arm, using 2-sided pairwise Pearson chi-square testing with the Bonferroni corrected significance level of 0.017 (PASS, Version 08.0.8, NCSS Kaysville, Utah 2008). Assuming no loss to follow-up and complete data, the required sample size for this study is therefore 55 subjects per arm, giving a total required sample size of 165 subjects. The study was terminated early because of ethical concerns after an interim analysis" **Adverse effects:** no serious adverse events **Funding:** "There was no outside funding for this study" **Declarations/conflicts of interest:** "No conflict of interest for all authors" **Data handling by review authors:** the oral mucositis incidence of each WHO grade was presented as percentages so we converted this to numbers of persons experiencing each grade **Other information of note:** only abstracts available but the authors have provided extra information through email correspondence to allow inclusion in this review. Study report is currently being written up and secondary outcome data have not yet been analysed, so we will include these in the next update of the review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "were randomized to the above mentioned groups" Correspondence: "The computer program used to generate these sheets makes block stratified assignments with user selected block size" Comment: adequate method of random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "were randomized to the above mentioned groups" Correspondence: "The random sequence list was kept at the principal investigator's office and only when a subject had signed the informed consent and agrees to participate in any of the three arms of the study, was the research coordinator able to look at the list and assigned the treatment" Comment: these methods should have ensured that the allocation sequence was not manipulated

Toro 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel to allocated groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	The subjective elements in the scale used to measure oral mucositis could have introduced bias into the assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	This domain is not yet applicable as the study report is currently being written up
Other bias	Low risk	No other sources of bias are apparent

Zhang 2011

Methods	**Trial design:** parallel (4 arms) **Location:** Beijing, China **Number of centres:** 1 **Study duration:** June 2009 to May 2010
Participants	**Inclusion criteria:** patients due to receive high-dose MTX **Exclusion criteria:** not reported **Cancer type:** osteosarcoma (bone cancer) **Cancer treatment:** MTX plus vincristine plus LV **Any other potentially important prognostic factors:** not reported **Age at baseline (years):** not reported **Gender:** not reported **Number randomised:** 147 (Gp A: 52; Gp B: 66; Gp C: 29) (numbers are for the 3 groups of interest to this review) **Number evaluated:** 147 (Gp A: 52; Gp B: 66; Gp C: 29)
Interventions	**Comparison: cryotherapy versus LV versus high dose LV** The 4th group involved using the standard LV dose once OM symptoms appeared. This constitutes treatment rather than prevention and therefore we excluded this arm **Gp A:** from the start of MTX, 100 ml ice water to be used for gargling (amount per gargle and frequency of gargling not specified), for 3 consecutive days **Gp B:** from the start of MTX, 3 mg LV dissolved in 100 ml water to be used for gargling per day, for 3 consecutive days (amount per gargle not specified) **Gp C:** from the start of MTX, 200 mg LV dissolved in 40 ml water to be used for gargling per day (10 ml 4 times daily), for 3 consecutive days

Zhang 2011 *(Continued)*

	All participants received MTX (10 g/m^2 administered by IV over 4 to 6 hours), vincristine (2 mg), and LV (12 mg every 6 hours, beginning 6 to 8 hours after finishing the MTX IV drop - it is not clear from the translation of the paper how long this occurred for or indeed if was just a single dose 6 to 8 hour after MTX). From 1 day prior to the start of MTX, participants had diuresis and alkalinising for 3 consecutive days, plus oral sodium bicarbonate (1 g) and allopurinol (200 mg) both 3 times daily for 4 consecutive days **Compliance:** not reported **Duration of treatment (intended):** 3 days (actual length of time the ice water or LV was held in the mouth is not reported)
Outcomes	• Oral mucositis: WHO and NCI-CTC (3.0) 0 to 4 scale (assessed 1 and 10 days after start of chemotherapy - reported as incidence of any OM over the study period and also by severity on the 4th day after MTX) • Duration of oral mucositis (not an outcome of this review) • MTX concentration in saliva (not an outcome of this review)
Notes	**Sample size calculation:** not reported **Adverse effects:** not reported **Funding:** not reported/not obtained from translation **Declarations/conflicts of interest:** not reported/not obtained from translation **Data handling by review authors:** we have used the data from Table 1 for the analysis of no mucositis versus any mucositis as this appears to be the incidence of any mucositis over the whole study period, and is therefore not at risk of bias; we have used the data on severity at day 4 but it may be at risk of bias due to selective reporting and readers should take this into consideration when interpreting the results **Other information of note:** it is unclear why the authors report OM severity at day 4, after they state that symptoms usually occur 5 to 7 days after chemotherapy. No participants had severe OM (grades 3 or 4) on day 4. If any participants developed severe OM after day 4, then the study will not reflect this and the incidence of severe OM in this type of study will have been underestimated. We would recommend that authors report the maximum grade experienced by each participant in future publications, or at least report a range of appropriate time points

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated to 4 groups using a random number table" Comment: random sequence appears to have been adequately generated
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomly allocated to 4 groups using a random number table" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel to allocated groups
Blinding of outcome assessment (detection bias)	High risk	The subjective elements in the scales used to measure oral mucositis could have introduced bias into the assessments

Zhang 2011 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	High risk	Oral mucositis was measured on the day of chemotherapy and on day 10, but severity is reported on day 4
Other bias	Low risk	No other sources of bias are apparent

5FU = fluorouracil; autologous = patients' own cells; allogeneic = cells from donor; BMI = body mass index; BMT = bone marrow transplantation; CI = confidence interval; EOCG = Eastern Oncology Co-operative Group; GVHD = graft-versus-host disease; HSCT = haematopoietic stem cell transplantation; IFN = interferon; IV = intravenous; LV = leucovorin; MD = mean difference; MTX = methotrexate; NCI-CTC = National Cancer Institute common toxicity criteria; OM = oral mucositis; OMAS = oral mucositis assessment scale; PBSCT = peripheral blood stem cell transplantation; SCT = stem cell transplantation; SD = standard deviation; TPN = total parenteral nutrition; URD = unrelated donor; VAS = visual analogue scale; VP16 = vepesid/etoposide; WHO = World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aisa 2005	Not RCT (historical controls)
Baydar 2005	Cross-over study. First-period data not presented
Castelino 2011	Plain versus flavoured ice. Cross-over study. First-period data not presented
de Paula Eduardo 2014	Cryotherapy plus laser versus laser. We cannot exclude the possibility of interaction between interventions and therefore we would not be confident in stating that any improved/reduced effect is due to the cryotherapy
Karagozoglu 2005	Not RCT (participants were allocated by alternation)
Mori 2006	Not RCT (historical controls)
Nikoletti 2005	Plain versus flavoured ice versus standard care. Cross-over study. First-period data not presented
Ohyama 1994	Translated from Japanese: case series of 5 cancer patients
Papadeas 2007	Not RCT (allocation based on date of birth)
Sato 1997	Unclear if RCT. Author was contacted during previous update of this Cochrane review but we received no response
Sato 2006	Not RCT (no mention of random allocation to groups)

RCT = randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

CTRI/2013/08/003906

Methods	**Trial design:** parallel (2 arms)
	Location: Chandigarh, India

CTRI/2013/08/003906 *(Continued)*

	Number of centres: 1 **Study duration:** 6 months (dates unclear from trials registry)
Participants	**Inclusion criteria:** aged from 18 to 80 years; males or females newly diagnosed with head and neck cancer; radical radiotherapy planned; normal mucosa **Exclusion criteria:** palliative radiotherapy planned; coming for booster dose of radiation **Cancer type:** head and neck **Cancer treatment:** radiotherapy to the head and neck **Any other potentially important prognostic factors:** unclear from trials registry **Age at baseline (years):** unclear from trials registry **Gender:** unclear from trials registry **Number randomised:** 60 (Gp A: 30; Gp B: 30) **Number evaluated:** unclear from trials registry
Interventions	**Comparison: cryotherapy versus no treatment** **Gp A:** ice cubes held in mouth for 4 min before radiotherapy and for a further 4 min after the session **Gp B:** standard oral care All participants received standard oral care **Compliance:** unclear from trials registry **Duration of treatment:** unclear from trials registry
Outcomes	• Oral mucositis: WHO 0 to 4 scale (assessed on days 5, 10, 15 and 20) • Tumour size and response (not an outcome of this review)
Notes	**Emailed study investigators 29/06/2015 for publication details or full unpublished study data** **Response:** "This was an M.Sc dissertation by a student from the institute of nursing and I was one of the guides. I shall try and contact this student for complete details and then get back to you. With regards, Sushmita Ghoshal" **Status:** still awaiting further details and therefore unable to include these valuable data in the review

Lu 2013

Methods	**Trial design:** parallel (2 arms) **Location:** Suzhou, China **Number centres:** 1

Lu 2013 *(Continued)*

	Study duration: unclear from abstract
Participants	**Inclusion criteria:** unclear from abstract **Exclusion criteria:** unclear from abstract **Cancer type:** unclear from abstract **Cancer treatment:** unclear from abstract (followed by HSCT) **Any other potentially important prognostic factors:** unclear from abstract **Age at baseline (years):** unclear from abstract **Gender:** unclear from abstract **Number randomised:** 37 (number per group unclear from abstract) **Number evaluated:** unclear from abstract
Interventions	**Comparison: full cryotherapy versus partial cryotherapy** **Gp A:** oral cryotherapy from the beginning of chemotherapy infusion until the end of infusion **Gp B:** oral cryotherapy starting half way through chemotherapy infusion until the end of infusion All participants received basic oral care **Compliance:** unclear from abstract **Duration of treatment:** unclear from abstract
Outcomes	• Oral mucositis: NCI-CTC 0 to 4 scale • Duration of oral mucositis (not an outcome of this review)
Notes	**Unable to obtain email addresses for study investigators. Awaiting publication of full trial report**

NCT01653106

Methods	**Trial design:** parallel (2 arms) **Location:** Columbus, Ohio, USA **Number of centres:** 1 **Study duration:** April 2012 to March 2015
Participants	**Inclusion criteria:** minimum 18 years of age; diagnosed with multiple myeloma and due to receive autologous STC **Exclusion criteria:** any other medical condition (including mental illness or substance abuse) which may interfere with ability to give informed consent, co-operate, and participate in the study, or which may interfere with the interpretation of the results **Cancer type:** haematological (multiple myeloma) **Cancer treatment:** high-dose melphalan followed by autologous SCT **Any other potentially important prognostic factors:** unclear from trials registry **Age at baseline (years):** unclear from trials registry

NCT01653106 *(Continued)*

	Gender: unclear from trials registry **Number randomised:** 146 (Gp A: 73; Gp B: 73) **Number evaluated:** unclear from trials registry
Interventions	**Comparison: 2 hours of cryotherapy versus 6 hours of cryotherapy** **Gp A:** 1 ounce of shaved ice placed in mouth starting 15 min before receiving chemotherapy, and replenished for 2 hours **Gp B:** 1 ounce of shaved ice placed in mouth starting 15 min before receiving chemotherapy, and replenished for 6 hours **Compliance:** unclear from trials registry **Duration of treatment:** 2 hours or 6 hours
Outcomes	• Oral mucositis: NCI-CTC (4.0) 0 to 4 scale (incidence of severe mucositis i.e. grade 3 to 4, assessed over 21 days) • Melphalan pharmacokinetic modelling (not an outcome of this review)
Notes	**Emailed study investigators 24/09/2015 for publication details or full unpublished study data**

Robenolt 2010

Methods	**Trial design:** parallel (2 arms) **Location:** USA **Number of centres:** unclear from abstract **Study duration:** unclear from abstract
Participants	**Inclusion criteria:** unclear from abstract **Exclusion criteria:** unclear from abstract **Cancer type:** unclear from abstract **Cancer treatment:** high-dose melphalan (> 140 mg/m^2) either alone or as part of the BEAM regimen, prior to autologous HSCT **Any other potentially important prognostic factors:** unclear from abstract **Age at baseline (years):** unclear from abstract **Gender:** unclear from abstract **Number randomised:** 40 (number per group unclear from abstract) **Number evaluated:** unclear from abstract
Interventions	**Comparison: cryotherapy versus no treatment** **Gp A:** oral cryotherapy 5 min before the start of chemotherapy infusion, continuing until 30 min after the completion of infusion **Gp B:** chemotherapy only **Compliance:** unclear from abstract

Robenolt 2010 *(Continued)*

	Duration of treatment: unclear from abstract
Outcomes	• Oral mucositis: WHO 0 to 4 scale (assessed over 14 days) • Oral pain: scale not reported (assessed over 14 days) • Patient functioning: swallowing, eating, and talking (not outcomes of this review)
Notes	**Emailed study investigators 29/09/2015 for publication details or full unpublished study data**

Xourafas 2009

Methods	**Trial design:** parallel (2 arms) **Location:** unclear from abstract **Number of centres:** unclear from abstract **Study duration:** unclear from abstract
Participants	**Inclusion criteria:** minimum 18 years of age **Exclusion criteria:** unclear from abstract **Cancer type:** breast **Cancer treatment:** super intensive chemotherapy (various types) **Any other potentially important prognostic factors:** unclear from abstract **Age at baseline (years):** unclear from abstract **Gender:** females **Number randomised:** 150 (number per group unclear from abstract) **Number evaluated:** unclear from abstract
Interventions	**Comparison: cryotherapy versus control (unclear from abstract)** **Gp A:** details of regimen not described in abstract **Gp B:** details of regimen not described in abstract **Compliance:** unclear from abstract **Duration of treatment (intended):** unclear from abstract
Outcomes	• Duration of opioid use (fentanyl) • Oral pain (assessed verbally daily)
Notes	**Emailed study investigators 29/09/2015 for publication details or full unpublished study data**

autologous = patients' own cells; HSCT = haematopoietic stem cell transplantation; NCI-CTC = National Cancer Institute common toxicity criteria; SCT = stem cell transplantation; WHO = World Health Organization

Characteristics of ongoing studies *[ordered by study ID]*

NCT01789658

Trial name or title	A randomized controlled trial of cryotherapy for prevention and reduction of severity of oral mucositis in children undergoing hematopoietic stem cell transplantation
Methods	**Trial design:** parallel (2 arms) **Location:** unclear from trials registry **Number of centres:** unclear from trials registry **Study duration:** October 2012 to estimated September 2015
Participants	**Inclusion criteria:** aged between 4 and 18 years; due to receive chemotherapy as conditioning treatment prior to HSCT in Sweden; sufficient knowledge of Swedish to understand the protocols **Exclusion criteria:** not reported **Cancer type:** haematological (multiple myeloma) **Cancer treatment:** chemotherapy prior to HSCT **Any other potentially important prognostic factors:** unclear from trials registry **Age at baseline (years):** 4 to 18 **Gender:** unclear from trials registry **Number randomised:** 50 (estimated enrolment - not reported by group) **Number evaluated:** unclear from trials registry
Interventions	**Comparison: cryotherapy versus standard oral care** **Gp A:** ice chips/ice cream/ice water used during chemotherapy infusion, replenished continuously (children receiving a 24-hour infusion instructed to use cryotherapy for 1 hour, 4 times per day) **Gp B:** standard oral care **Compliance:** unclear from trials registry **Duration of treatment:** unclear from trials registry
Outcomes	• Oral mucositis: 1) WHO 0 to 4 scale (assessed daily until HSCT, for expected average of 20 days); 2) ChiMES 0 to 23 scale (assessed daily by parent and child until HSCT, for expected average of 20 days) • Oral pain (assessed daily by nurse until HSCT, for expected average of 20 days) • Quality of life: emotional and psychological status using Beck youth inventories for depression and anxiety (assessed daily until HSCT, for expected average of 20 days) • Duration and dose of opioid use (during hospitalisation in connection with HSCT, for expected average of 25 days) • Normalcy of diet: duration of TPN (during hospitalisation in connection with HSCT, for expected average of 25 days) • Duration of hospital stay (in connection with HSCT) • Pain (general: not an outcome of this review) • Weight loss (not an outcome of this review) • Duration of antibiotic treatment (not an outcome of this review) • Duration of febrile neutropenia (not an outcome of this review) • C-reactive protein level (not an outcome of this review) • S-Albumin (not an outcome of this review)
Starting date	October 2012

NCT01789658 *(Continued)*

Contact information	Gustaf Ljungman (gustaf.ljungman@kbh.uu.se); Tove Kamsvåg Magnusson (tove.kamsvag_magnusson@gmail.com)
Notes	

NCT02326675

Trial name or title	Randomized controlled, open-label study on the use of cryotherapy in the prevention of chemotherapy-induced mucositis in stem cell transplant patients
Methods	**Trial design:** parallel (2 arms) **Location:** Florida, USA **Number of centres:** unclear from trials registry **Study duration:** March 2015 to estimated March 2019
Participants	**Inclusion criteria:** minimum 18 years of age; due to receive etoposide chemotherapy (minimum dose of 30 mg/kg) as conditioning treatment prior to autologous SCT **Exclusion criteria:** prior radiation to head and neck; known oropharynx involvement in malignancy; history of non-compliance or lack capacity to give informed consent **Cancer type:** unclear from trials registry **Cancer treatment:** etoposide (minimum dose of 30 mg/kg) prior to autologous SCT **Any other potentially important prognostic factors:** unclear from trials registry **Age at baseline (years):** unclear from trials registry **Gender:** unclear from trials registry **Number randomised:** 48 (estimated enrolment - not reported by group) **Number evaluated:** unclear from trials registry
Interventions	**Comparison: cryotherapy versus no treatment** **Gp A:** ice chips/other very cold or frozen food used starting 15 min before starting etoposide infusion for a 30-min period, then 3 saline rinses over 15-min period. This alternating cycle is repeated until 30 min after completion of etoposide infusion (total 150 min) **Gp B:** at start of etoposide infusion 3 saline rinses over 15-min period followed by 30-rest period (no treatment). This alternating cycle is repeated until 30 min after completion of etoposide infusion (total 150 min) All participants will receive standard oral care (saline rinses) **Compliance:** unclear from trials registry **Duration of treatment:** 150 min
Outcomes	• Oral mucositis: scale not reported (assessed starting on day +1 post-transplant until discharged from hospital, for expected average of 21 to 28 days) • Time to onset of oral mucositis (not an outcome of this review) • Duration of oral mucositis (not an outcome of this review)

NCT02326675 *(Continued)*	• Compliance: number of participants that tolerate cryotherapy during each infusion (not an outcome of this review but we will record the information in the 'Characteristics of included studies' tables)
Starting date	March 2015
Contact information	Christina Cline (clcline@ufl.edu); Leslie Pettiford (lpettiford@ufl.edu)
Notes	

autologous = patients' own cells; ChiMES = Children's International Mucositis Evaluation Scale; HSCT = haematopoietic stem cell transplantation; SCT = stem cell transplantation; TPN = total parenteral nutrition; WHO = World Health Organization

DATA AND ANALYSES

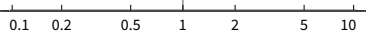
Comparison 1. Cryotherapy versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Fluorouracil (5FU) treatment	5	444	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.52, 0.72]
1.2 High-dose melphalan treatment prior to stem cell transplantation	5	270	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.35, 1.01]
1.3 Methotrexate treatment post-stem cell transplantation to prevent GVHD	1	122	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.90, 1.07]
2 Oral mucositis (moderate + severe)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Fluorouracil (5FU) treatment	5	444	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.41, 0.65]
2.2 High-dose melphalan treatment prior to stem cell transplantation	5	270	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.17, 1.09]
2.3 Methotrexate treatment post-stem cell transplantation to prevent GVHD	1	122	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.85, 1.20]
3 Oral mucositis (severe)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Fluorouracil (5FU) treatment	5	444	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.27, 0.61]
3.2 High-dose melphalan treatment prior to stem cell transplantation	5	270	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.20, 0.72]
3.3 Methotrexate treatment post-stem cell transplantation to prevent GVHD	1	122	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.61, 1.25]
4 Interruptions to cancer treatment	1	80	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.20, 0.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Interruptions to cancer treatment (days of interruption)	1	80	Mean Difference (IV, Random, 95% CI)	-8.0 [-9.26, -6.74]
6 Oral pain (0 to 10 scale)	2	85	Mean Difference (IV, Random, 95% CI)	-1.50 [-2.11, -0.89]
7 Normalcy of diet (days of total parenteral nutrition)	1	78	Mean Difference (IV, Random, 95% CI)	-2.18 [-4.33, -0.03]
8 Duration of hospitalisation (days)	2	123	Mean Difference (IV, Random, 95% CI)	-1.39 [-2.97, 0.19]
9 Duration of opioid use (days)	1	78	Mean Difference (IV, Random, 95% CI)	-2.28 [-5.33, 0.77]

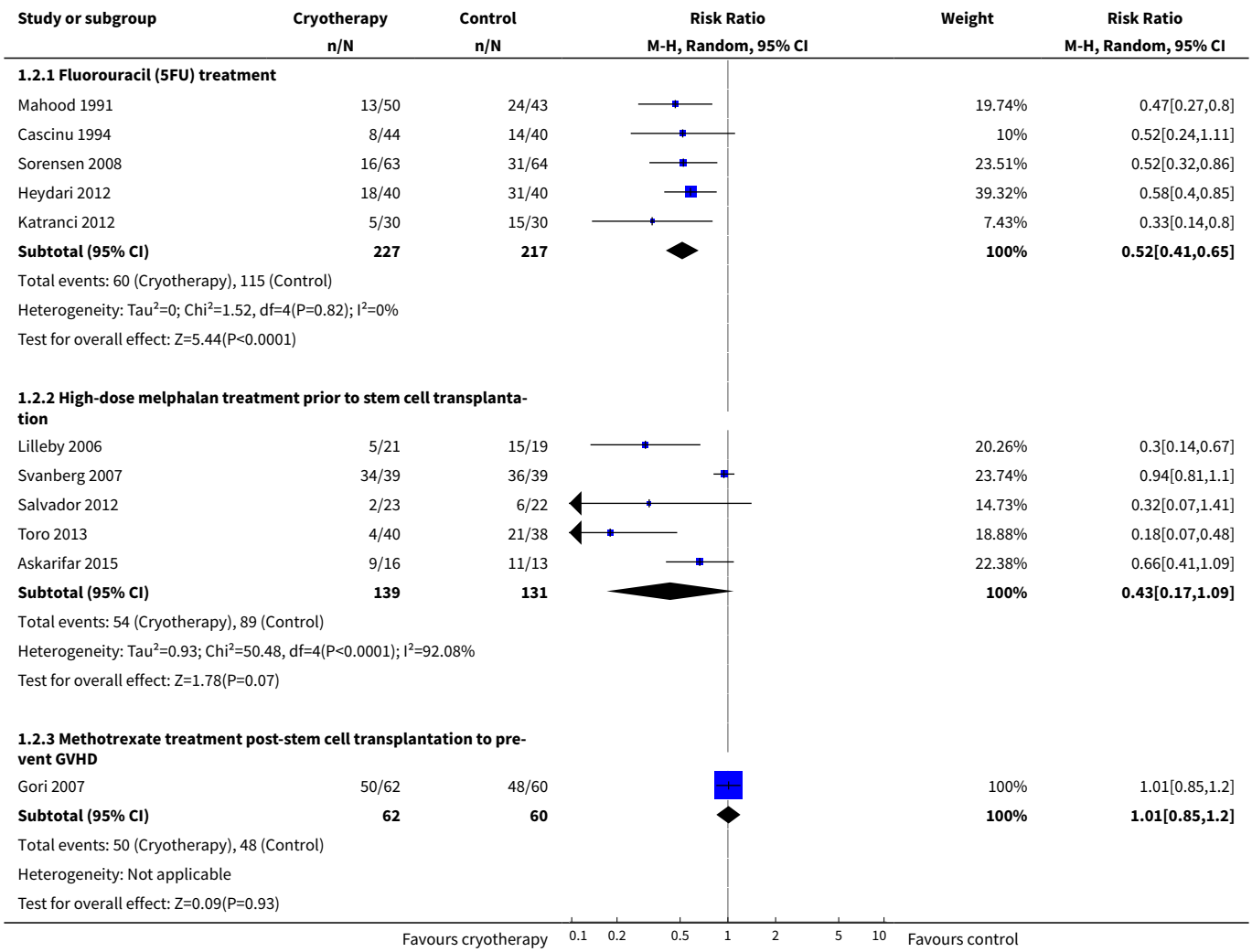
Analysis 1.1. Comparison 1 Cryotherapy versus control, Outcome 1 Oral mucositis (any).

Study or subgroup	Cryotherapy n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Fluorouracil (5FU) treatment					
Mahood 1991	22/50	35/43		22.61%	0.54[0.38,0.76]
Cascinu 1994	14/44	20/40		9.44%	0.64[0.37,1.08]
Sorensen 2008	34/63	49/64		37.98%	0.7[0.54,0.92]
Katranci 2012	12/30	23/30		11.57%	0.52[0.32,0.84]
Heydari 2012	18/40	31/40		18.4%	0.58[0.4,0.85]
Subtotal (95% CI)	**227**	**217**		**100%**	**0.61[0.52,0.72]**
Total events: 100 (Cryotherapy), 158 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.12, df=4(P=0.71); I^2=0%					
Test for overall effect: Z=5.87(P<0.0001)					
1.1.2 High-dose melphalan treatment prior to stem cell transplantation					
Lilleby 2006	13/21	19/19		22.11%	0.63[0.45,0.88]
Svanberg 2007	35/39	36/39		23.88%	0.97[0.85,1.12]
Salvador 2012	6/23	15/22		16.47%	0.38[0.18,0.81]
Toro 2013	4/40	25/38		13.61%	0.15[0.06,0.4]
Askarifar 2015	16/16	13/13		23.93%	1[0.88,1.14]
Subtotal (95% CI)	**139**	**131**		**100%**	**0.59[0.35,1.01]**
Total events: 74 (Cryotherapy), 108 (Control)					
Heterogeneity: Tau^2=0.3; Chi^2=87.07, df=4(P<0.0001); I^2=95.41%					
Test for overall effect: Z=1.93(P=0.05)					
1.1.3 Methotrexate treatment post-stem cell transplantation to prevent GVHD					
Gori 2007	58/62	57/60		100%	0.98[0.9,1.07]
Subtotal (95% CI)	**62**	**60**		**100%**	**0.98[0.9,1.07]**
Total events: 58 (Cryotherapy), 57 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.35(P=0.73)					

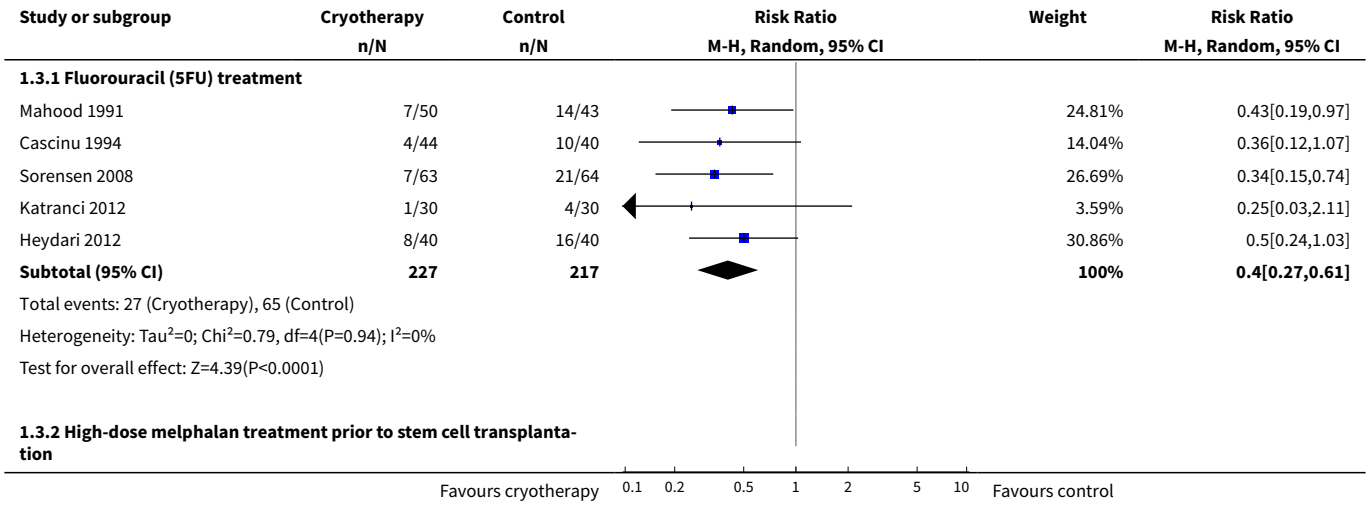


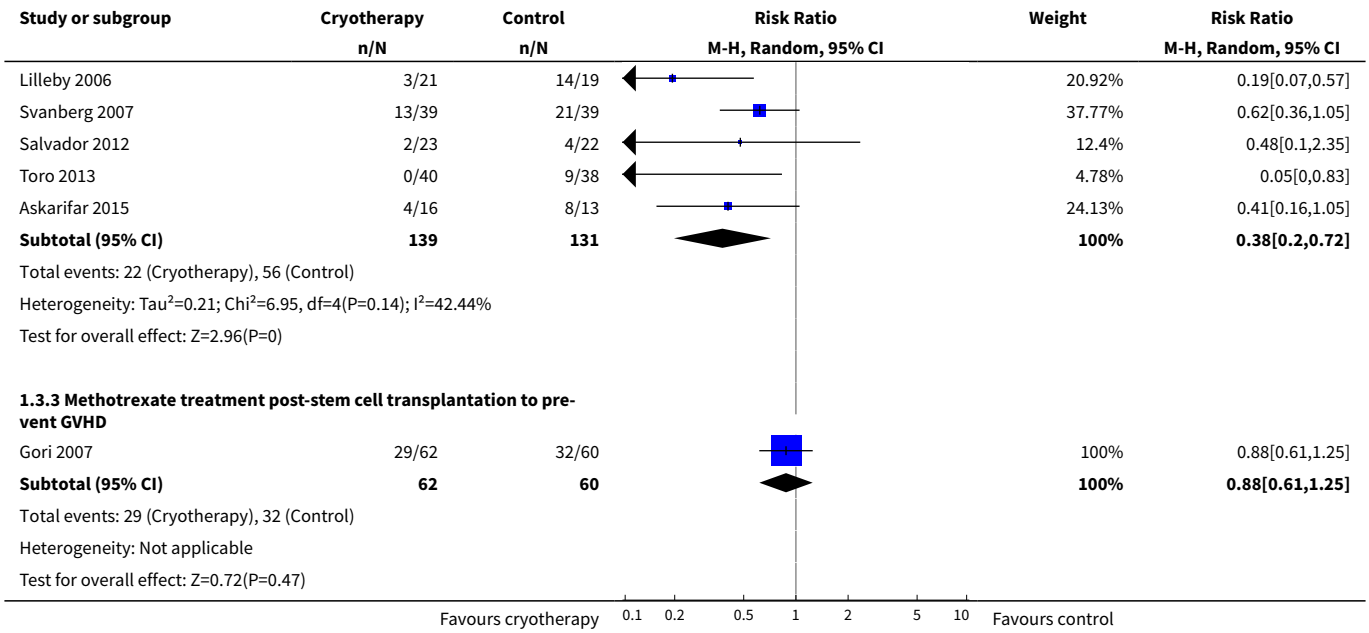
Favours cryotherapy — Favours control

Analysis 1.2. Comparison 1 Cryotherapy versus control, Outcome 2 Oral mucositis (moderate + severe).

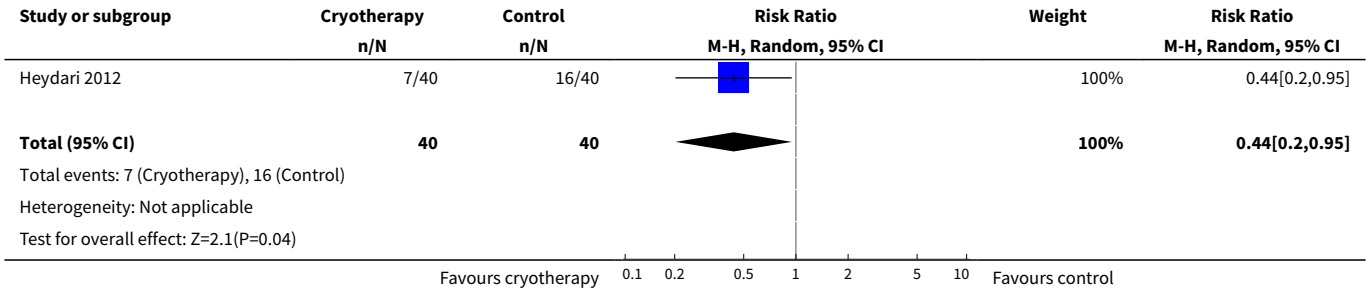


Analysis 1.3. Comparison 1 Cryotherapy versus control, Outcome 3 Oral mucositis (severe).

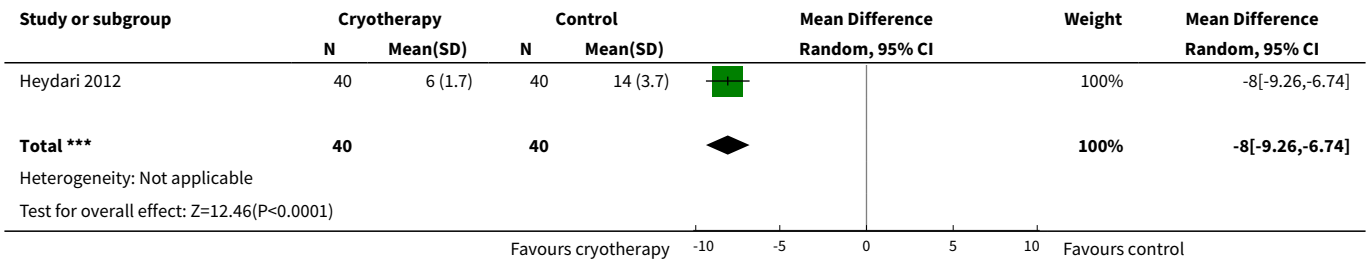




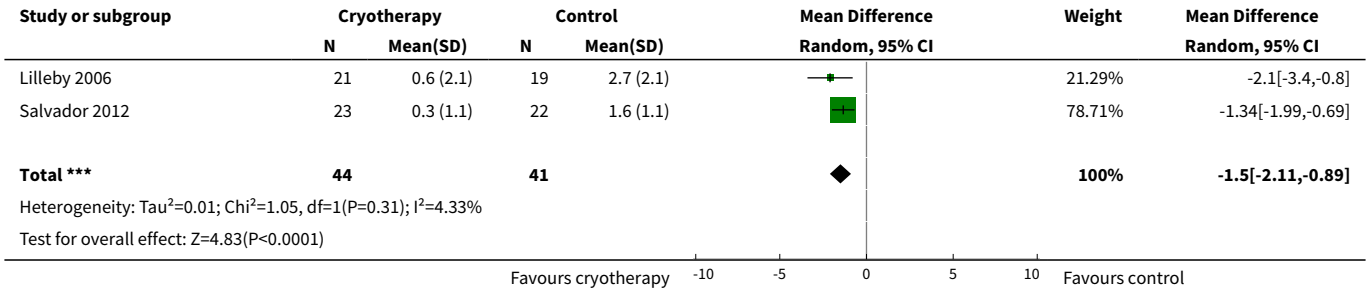
Analysis 1.4. Comparison 1 Cryotherapy versus control, Outcome 4 Interruptions to cancer treatment.



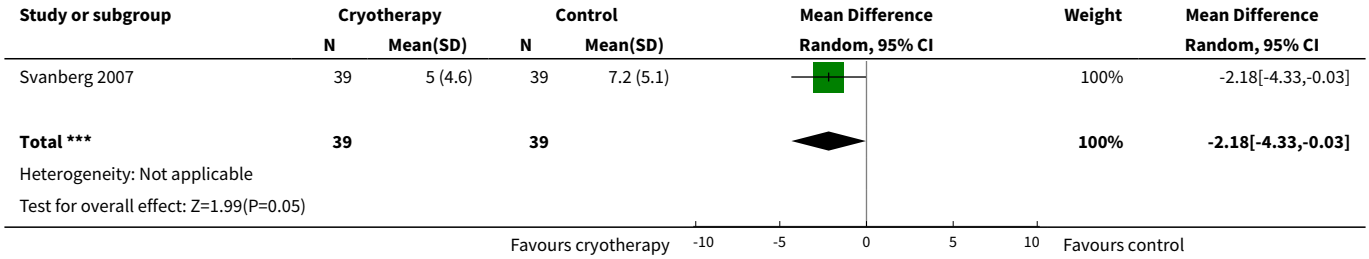
Analysis 1.5. Comparison 1 Cryotherapy versus control, Outcome 5 Interruptions to cancer treatment (days of interruption).



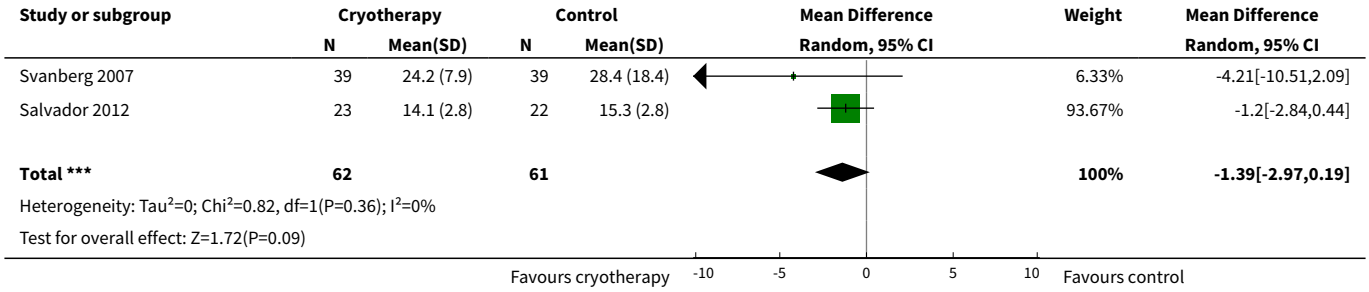
Analysis 1.6. Comparison 1 Cryotherapy versus control, Outcome 6 Oral pain (0 to 10 scale).



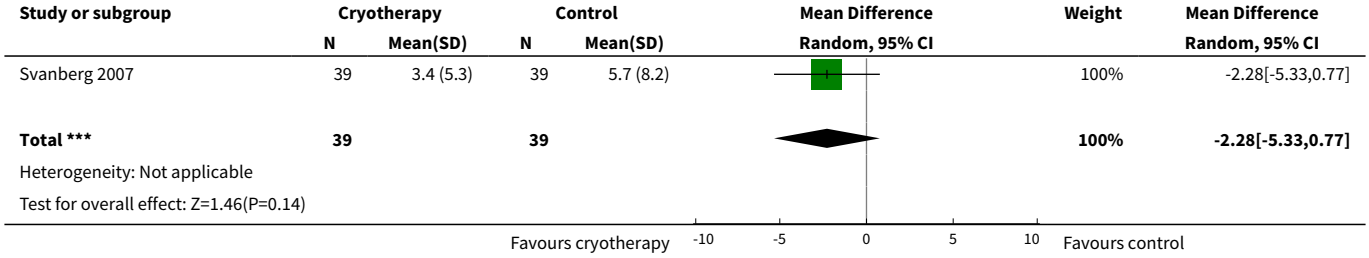
Analysis 1.7. Comparison 1 Cryotherapy versus control, Outcome 7 Normalcy of diet (days of total parenteral nutrition).



Analysis 1.8. Comparison 1 Cryotherapy versus control, Outcome 8 Duration of hospitalisation (days).



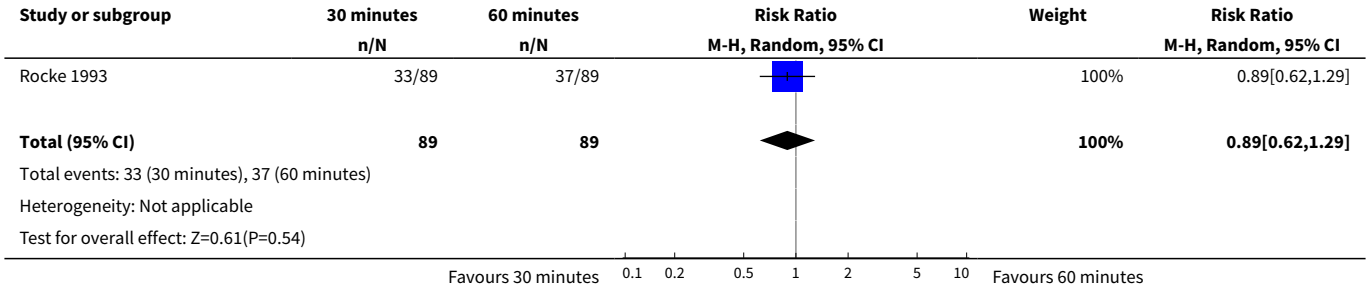
Analysis 1.9. Comparison 1 Cryotherapy versus control, Outcome 9 Duration of opioid use (days).



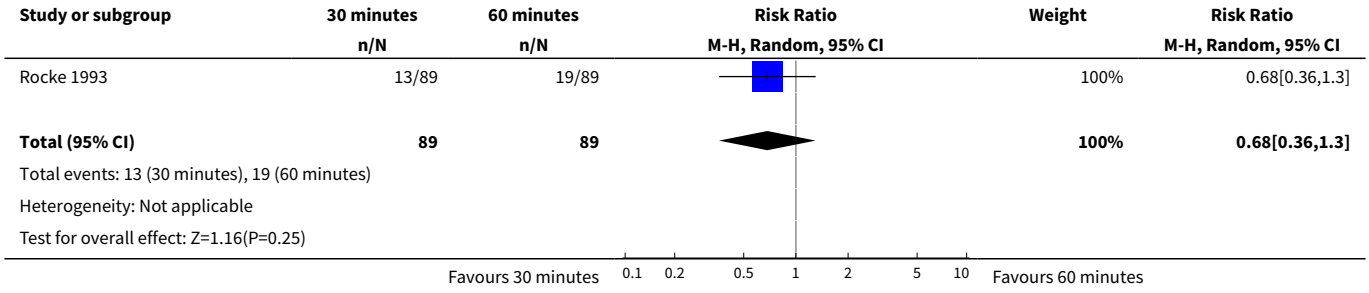
Comparison 2. Different oral cryotherapy regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	1	178	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.62, 1.29]
2 Oral mucositis (moderate + severe)	1	178	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.36, 1.30]
3 Oral mucositis (severe)	1	178	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.23, 1.58]

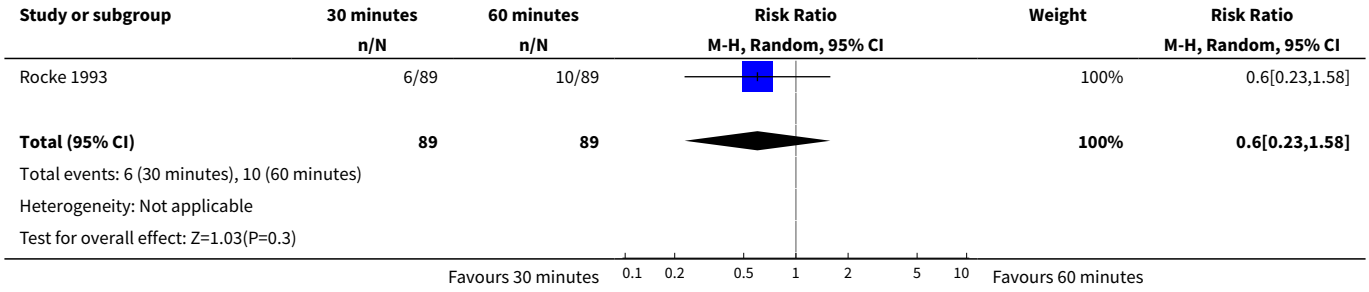
Analysis 2.1. Comparison 2 Different oral cryotherapy regimens, Outcome 1 Oral mucositis (any).



Analysis 2.2. Comparison 2 Different oral cryotherapy regimens, Outcome 2 Oral mucositis (moderate + severe).



Analysis 2.3. Comparison 2 Different oral cryotherapy regimens, Outcome 3 Oral mucositis (severe).



Comparison 3. Cryotherapy versus chlorhexidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	1	133	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.71, 1.32]
2 Oral mucositis (moderate + severe)	1	133	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.51, 1.56]
3 Oral mucositis (severe)	1	133	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.34, 2.18]

Analysis 3.1. Comparison 3 Cryotherapy versus chlorhexidine, Outcome 1 Oral mucositis (any).

Study or subgroup	Cryotherapy n/N	Chlorhexidine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Sorensen 2008	34/63	39/70		100%	0.97[0.71,1.32]
Total (95% CI)	**63**	**70**		**100%**	**0.97[0.71,1.32]**
Total events: 34 (Cryotherapy), 39 (Chlorhexidine)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.2(P=0.84)					

Favours cryotherapy — Favours chlorhexidine

Analysis 3.2. Comparison 3 Cryotherapy versus chlorhexidine, Outcome 2 Oral mucositis (moderate + severe).

Study or subgroup	Cryotherapy n/N	Chlorhexidine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Sorensen 2008	16/63	20/70		100%	0.89[0.51,1.56]
Total (95% CI)	**63**	**70**		**100%**	**0.89[0.51,1.56]**
Total events: 16 (Cryotherapy), 20 (Chlorhexidine)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.41(P=0.68)					

Favours cryotherapy — Favours chlorhexidine

Analysis 3.3. Comparison 3 Cryotherapy versus chlorhexidine, Outcome 3 Oral mucositis (severe).

Study or subgroup	Cryotherapy n/N	Chlorhexidine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Sorensen 2008	7/63	9/70		100%	0.86[0.34,2.18]
Total (95% CI)	**63**	**70**		**100%**	**0.86[0.34,2.18]**
Total events: 7 (Cryotherapy), 9 (Chlorhexidine)					
Heterogeneity: Not applicable					

Favours cryotherapy — Favours chlorhexidine

Study or subgroup	Cryotherapy n/N	Chlorhexidine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.31(P=0.76)					

Favours cryotherapy 0.1 0.2 0.5 1 2 5 10 Favours chlorhexidine

Comparison 4. Cryotherapy versus leucovorin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Low-dose leucovorin (3 mg daily)	1	118	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.90]
1.2 High-dose leucovorin (200 mg daily)	1	81	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.47, 0.90]
2 Oral mucositis (moderate + severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Low-dose leucovorin (3 mg daily)	1	118	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.01, 3.42]
2.2 High-dose leucovorin (200 mg daily)	1	81	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Oral mucositis (severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Low-dose leucovorin (3 mg daily)	1	118	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 High-dose leucovorin (200 mg daily)	1	81	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Cryotherapy versus leucovorin, Outcome 1 Oral mucositis (any).

Study or subgroup	Cryotherapy n/N	Leucovorin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Low-dose leucovorin (3 mg daily)					
Zhang 2011	27/52	51/66		100%	0.67[0.5,0.9]
Subtotal (95% CI)	**52**	**66**		**100%**	**0.67[0.5,0.9]**
Total events: 27 (Cryotherapy), 51 (Leucovorin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.66(P=0.01)					
4.1.2 High-dose leucovorin (200 mg daily)					
Zhang 2011	27/52	23/29		100%	0.65[0.47,0.9]
Subtotal (95% CI)	**52**	**29**		**100%**	**0.65[0.47,0.9]**

Favours cryotherapy 0.1 0.2 0.5 1 2 5 10 Favours leucovorin

Study or subgroup	Cryotherapy n/N	Leucovorin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 27 (Cryotherapy), 23 (Leucovorin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.59(P=0.01)					

Favours cryotherapy 0.1 0.2 0.5 1 2 5 10 Favours leucovorin

Analysis 4.2. Comparison 4 Cryotherapy versus leucovorin, Outcome 2 Oral mucositis (moderate + severe).

Study or subgroup	Cryotherapy n/N	Leucovorin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Low-dose leucovorin (3 mg daily)					
Zhang 2011	0/52	3/66		100%	0.18[0.01,3.42]
Subtotal (95% CI)	**52**	**66**		**100%**	**0.18[0.01,3.42]**
Total events: 0 (Cryotherapy), 3 (Leucovorin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.14(P=0.25)					
4.2.2 High-dose leucovorin (200 mg daily)					
Zhang 2011	0/52	0/29			Not estimable
Subtotal (95% CI)	**52**	**29**			**Not estimable**
Total events: 0 (Cryotherapy), 0 (Leucovorin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					

Favours cryotherapy 0.1 0.2 0.5 1 2 5 10 Favours leucovorin

Analysis 4.3. Comparison 4 Cryotherapy versus leucovorin, Outcome 3 Oral mucositis (severe).

Study or subgroup	Cryotherapy n/N	Leucovorin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Low-dose leucovorin (3 mg daily)					
Zhang 2011	0/52	0/66			Not estimable
Subtotal (95% CI)	**52**	**66**			**Not estimable**
Total events: 0 (Cryotherapy), 0 (Leucovorin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.3.2 High-dose leucovorin (200 mg daily)					
Zhang 2011	0/52	0/29			Not estimable
Subtotal (95% CI)	**52**	**29**			**Not estimable**
Total events: 0 (Cryotherapy), 0 (Leucovorin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					

Favours cryotherapy 0.1 0.2 0.5 1 2 5 10 Favours leucovorin

ADDITIONAL TABLES

Table 1. Study data not included in analyses

Outcome	Study	Description of data	Cryotherapy	Control	Result
Oral mucositis	Kakoei 2013	WHO 0 to 4 scale; physician-judged rating used; day 14 data used due to highest control group mean (should be noted that on days 1 and 7 the cryotherapy group mean is higher but with no statistically significant difference)	n = 20 mean 0.95 (SD 0.58)	n = 20 mean 1.2 (SD 0.89)	MD -0.25 (95% CI -0.72 to 0.22); P = 0.29 (there is no evidence of a difference in mucositis severity)
Oral pain	Heydari 2012	1 to 5 scale: 1 = never, 2 = 1 day of week, 3 = 2 to 3 days of week, 4 = most of week, 5 = 7 days of week	n = 40 mean 1.71 (SD 0.74)	n = 40 mean 3.64 (SD 1.20)	MD -1.93 (95% CI -2.37 to -1.49); P < 0.00001 (cryotherapy statistically significantly reduced the duration of pain experience)
Normalcy of diet	Lilleby 2006	Days of TPN (we use the P value quoted in the study report)	n = 21 median 2 (range 0 to 15)	n = 19 median 5.5 (range 0 to 21)	P = 0.04 (cryotherapy statistically significantly reduced the number of days of TPN)
Number of days in hospital	Lilleby 2006	Days of hospitalisation (we use the P value quoted in the study report)	n = 21 median 9 (range 0 to 22)	n = 19 median 14 (range 0 to 30)	P = 0.11 (there is no evidence of a difference in the number of days of hospitalisation)
Number of days of treatment with opioid analgesics	Lilleby 2006	Days of IV narcotics (we use the P value quoted in the study report)	n = 21 median 0 (range 0 to 10)	n = 19 median 5.5 (range 0 to 13)	P = 0.0003 (cryotherapy statistically significantly reduced the number of days of IV narcotics)

CI = confidence interval; IV = intravenous; MD = mean difference; n = number of participants analysed; N/A = not applicable; SD = standard deviation; TPN = total parenteral nutrition

APPENDICES

Appendix 1. Cochrane Oral Health Group Trials Register search strategy

1 ((neoplasm* or cancer* or tumor* or tumour*):ti,ab) AND (INREGISTER)
2 ((leukaemi* or leukemi*):ti,ab) AND (INREGISTER)
3 ((malignan* or neutropeni* or carcino* or adenocarcinoma* or lymphoma*):ti,ab) AND (INREGISTER)
4 ((radioth* or radiat* or irradiat*):ti,ab) AND (INREGISTER)
5 (("bone marrow transplant*"):ti,ab) AND (INREGISTER)
6 ((chemo*):ti,ab) AND (INREGISTER)
7 (#1 or #2 or #3 or #4 or #5 or #6) AND (INREGISTER)
8 ((stomatitis or mucositis):ti,ab) AND (INREGISTER)
9 ((oral and mucos*):ti,ab) AND (INREGISTER)
10 ((mycosis or mycotic):ti,ab) AND (INREGISTER)
11 (mIAS:ti,ab) AND (INREGISTER)

12 (#8 or #9 or #10 or #11) AND (INREGISTER)
13 (cryotherap*:ti,ab) AND (INREGISTER)
14 ((ice or freez* or cold*):ti,ab) AND (INREGISTER)
15 (#13 or #14) AND (INREGISTER)
16 (#7 and #12 and #15) AND (INREGISTER)

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 [mh neoplasms]
#2 [mh leukemia]
#3 [mh lymphoma]
#4 [mh radiotherapy]
#5 [mh "antineoplastic agents"]
#6 (neoplasm* or cancer* or tumor* or tumour*)
#7 (leukaemi* or leukemi*)
#8 (malignan* or neutropeni* or carcino* or adenocarcinoma* or lymphoma*)
#9 "bone marrow transplant*"
#10 chemo*
#11 {or #1-#10}
#12 [mh stomatitis]
#13 [mh ^"candidiasis, oral"]
#14 stomatitis
#15 mucositis
#16 (oral near/6 mycos*)
#17 (mycosis or mycotic)
#18 mIAS:ti,ab
#19 {or #12-#18}
#20 [mh cryotherapy]
#21 cryotherap*
#22 (cold* or ice or freez*)
#23 {or #20-#22}
#24 #11 and #19 and #23

Appendix 3. MEDLINE (Ovid) search strategy

1. exp NEOPLASMS/
2. exp LEUKEMIA/
3. exp LYMPHOMA/
4. exp RADIOTHERAPY/
5. exp Antineoplastic agents/
6. Bone Marrow Transplantation/
7. neoplasm$.mp.
8. cancer$.mp.
9. (leukaemi$ or leukemi$).mp.
10. (tumour$ or tumor$).mp.
11. malignan$.mp.
12. neutropeni$.mp.
13. carcino$.mp.
14. adenocarcinoma$.mp.
15. lymphoma$.mp.
16. (radioth$ or radiat$ or irradiat$).mp.
17. (bone adj marrow adj5 transplant$).mp.
18. chemo$.mp.
19. or/1-18
20. exp STOMATITIS/
21. Candidiasis, Oral/
22. stomatitis.mp.
23. mucositis.mp.
24. (oral adj6 mucos$).mp.
25. (mycosis or mycotic).mp.
26. mIAS.ti,ab.
27. or/20-26
28. Cryotherapy/

29. cryotherap$.mp.
30. (cold or freez$ or ice).mp.
31. or/28-30
32. 19 and 27 and 31

Appendix 4. EMBASE (Ovid) search strategy

1. exp NEOPLASM/
2. exp LEUKEMIA/
3. exp LYMPHOMA/
4. exp RADIOTHERAPY/
5. exp Antineoplastic agent/
6. Bone Marrow Transplantation/
7. neoplasm$.mp.
8. cancer$.mp.
9. (leukaemi$ or leukemi$).mp.
10. (tumour$ or tumor$).mp.
11. malignan$.mp.
12. neutropeni$.mp.
13. carcino$.mp.
14. adenocarcinoma$.mp.
15. lymphoma$.mp.
16. (radioth$ or radiat$ or irradiat$).mp.
17. (bone adj marrow adj5 transplant$).mp.
18. chemo$.mp.
19. or/1-18
20. exp STOMATITIS/
21. Thrush/
22. stomatitis.mp.
23. mucositis.mp.
24. (oral adj6 mucos$).mp.
25. (mycosis or mycotic).mp.
26. mIAS.ti,ab.
27. or/20-26
28. Cryotherapy/
29. cryotherap$.mp.
30. (cold or freez$ or ice).mp.
31. or/28-30
32. 19 and 27 and 31

The above subject search was linked to the Cochrane Oral Health Group filter for identifying RCTs in EMBASE via Ovid:

1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (doubl$ adj blind$).ti,ab.
6. (singl$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.
9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16. 14 NOT 15

Appendix 5. CANCERLIT via PubMed search strategy

#31 (#19 and #26 and #30)
#30 (#27 or #28 or #29)

#29 ((cold* or freez* or ice))
#28 cryotherap*
#27 cryotherapy [mh:noexp]
#26 (#20 or #21 or #22 or #23 or #24 or #25)
#25 mIAS [tiab]
#24 (mycosis or mycotic)
#23 mucositis
#22 stomatitis
#21 oral candidiasis [mh:noexp]
#20 stomatitis [mh:exp]
#19 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#18 chemo*
#17 "bone marrow transplant*
#16 (radioth* or radiat* or irradiat*)
#15 lymphoma*
#14 adenocarcinoma*
#13 carcino*
#12 neutropeni*
#11 malignan*
#10 (tumor* or tumour*)
#9 (leukaemi* or leukemi*)
#8 cancer*
#7 neoplasm*
#6 bone marrow transplantation [mh:noexp]
#5 antineoplastic agents [mh:exp]
#4 radiotherapy [mh:exp]
#3 lymphoma [mh:exp]
#2 leukemia [mh:exp]
#1 neoplasm [mh:exp]

Appendix 6. CINAHL via EBSCO search strategy

S32 S19 and S27 and S31
S31 S28 or S29 or S30
S30 (cold* or ice or freez*)
S29 cryotherap*
S28 (mh "cryotherapy")
S27 S20 or S21 or S22 or S23 or S24 or S25 or S26
S26 TI mIAS OR AB mIAS
S25 (mycosis or mycotic)
S24 (oral N6 mucos*)
S23 mucositis
S22 stomatitis
S21 (mh "candidiasis, oral")
S20 (mh "stomatitis+")
S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18
S18 chemo*
S17 "bone marrow transplant*"
S16 (radioth* or radiat* or irradiat*)
S15 lymphoma*
S14 adenocarcinoma*
S13 carcino*
S12 neutropeni*
S11 malignan*
S10 (tumor* or tumour*)
S9 (leukaem* or leukem*)
S8 cancer*
S7 neoplasm*
S6 (MH "Bone marrow transplantation")
S5 (MH "Antineoplastic Agents+")
S4 (mh "radiotherapy+")
S3 (mh "lymphoma+")

S2 (mh "leukemia+")
S1 (mh "neoplasms+")

Appendix 7. US National Institutes of Health trials registry (ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform search strategies

mucositis and cryotherapy
mucositis and ice
mucositis and cold

Appendix 8. Oral mucositis measurement scales

Oral mucositis assessment scale (OMAS)

Oral cavity ulceration		Oral cavity erythema	
Grade 0	no lesion	**Grade 0**	none
Grade 1	lesion < 1 cm^2	**Grade 1**	not severe
Grade 2	lesion 1 to 3 cm^2	**Grade 2**	severe
Grade 3	lesion > 3 cm^2		

Ulceration and erythema are measured at 9 different sites and summated to give a total mucositis score

National Cancer Institute (NCI) common toxicity criteria (CTC) (as reported in Lilleby 2006)

Grade 0	no mucositis
Grade 1	painless ulcers, erythema or mild soreness without lesions
Grade 2	painful erythema, edema or ulcers but can swallow
Grade 3	painful erythema, edema or ulcers preventing swallowing or requiring hydration or total parenteral nutrition (feeding into vein rather than into gastrointestinal (GI) tract)
Grade 4	severe ulceration requiring prophylactic intubation

World Health Organization (WHO) scale (as reported in Gori 2007)

Grade 0	no mucositis
Grade 1	soreness ± erythema
Grade 2	erythema, ulcers. Patient can swallow solid diet
Grade 3	ulcers, extensive erythema. Patient cannot swallow solid diet
Grade 4	mucositis to the extent that alimentation is not possible

WHAT'S NEW

Date	Event	Description
26 January 2016	Amended	Minor edit (hyperlink)

CONTRIBUTIONS OF AUTHORS

Philip Riley: writing the Background and Methods sections, screening searches, data extraction, risk of bias assessment, interpreting the results, writing the review.
Anne-Marie Glenny: writing the Methods section, screening searches, data extraction, risk of bias assessment, interpreting the results.
Helen V Worthington: writing the Methods section, screening searches, data extraction, risk of bias assessment, interpreting the results.
Anne Littlewood: writing the Methods section, designing the search strategy and carrying out the searches, screening searches, data extraction, risk of bias assessment, interpreting the results.
Jan E Clarkson: interpreting the results and providing a clinical perspective.
Martin G McCabe: interpreting the results and providing a clinical perspective.

DECLARATIONS OF INTEREST

Philip Riley: I am a salaried member of the Cochrane Oral Health Group editorial team.
Anne-Marie Glenny: none known. I am Deputy Co-ordinating Editor of the Cochrane Oral Health Group.
Helen V Worthington: none know. I am Co-ordinating Editor of the Cochrane Oral Health Group.
Anne Littlewood: I am a salaried member of the Cochrane Oral Health Group editorial team.
Jan E Clarkson: none known. I am Co-ordinating Editor of the Cochrane Oral Health Group.
Martin G McCabe: none known. I am an Editor of the Cochrane Oral Health Group.

SOURCES OF SUPPORT

Internal sources

- School of Dentistry, The University of Manchester, UK.
- Manchester Academic Health Sciences Centre (MAHSC) and the NIHR Manchester Biomedical Research Centre, UK.

External sources

- National Institute for Health Research (NIHR), UK.

  This project was supported by the NIHR, via Cochrane Infrastructure funding to the Cochrane Oral Health Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health
- Cochrane Oral Health Group Global Alliance, Other.

  Through our Global Alliance (ohg.cochrane.org/partnerships-alliances), the Cochrane Oral Health Group has received support from: British Association for the Study of Community Dentistry, UK; British Association of Oral Surgeons, UK; British Orthodontic Society, UK; British Society of Paediatric Dentistry, UK; British Society of Periodontology, UK; Canadian Dental Hygienists Association, Canada; Mayo Clinic, USA; National Center for Dental Hygiene Research & Practice, USA; New York University College of Dentistry, USA; and Royal College of Surgeons of Edinburgh, UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- In the section 'Types of interventions', we have clarified that head-to-head studies assessing different oral cryotherapy regimens were also eligible. We have also clarified that studies looking at complex interventions (e.g. cryotherapy plus laser versus laser) will be excluded as we cannot rule out any important interaction between the two (or more) interventions.
- In the section 'Types of studies', we stated in the protocol that cross-over studies were to be excluded. However, in order to avoid losing valuable data, we treated such studies as parallel studies by only using first-period data.
- In the section 'Assessment of risk of bias in included studies', we stated in the protocol that we would not assess blinding of participants and personnel (performance bias), as it was not possible to use such blinding in any of the studies. We decided to include this domain of risk of bias in our assessments in order to give the reader a clearer picture of the problems with our confidence in the estimates of effect. This also affects the section 'Sensitivity analysis', as we are not able to carry out sensitivity analyses based on risk of bias.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [administration & dosage] [adverse effects]; Cryotherapy [*methods]; Fluorouracil [administration & dosage] [adverse effects]; Hematopoietic Stem Cell Transplantation; Melphalan [administration & dosage] [adverse effects]; Mouth Diseases [etiology] [therapy]; Myeloablative Agonists [administration & dosage] [adverse effects]; Neoplasms [*therapy]; Pain [etiology]; Randomized Controlled Trials as Topic; Stomatitis [chemically induced] [*prevention & control]

MeSH check words

Adult; Humans