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Amifostine for salivary glands in high-dose radioactive iodine treated differentiated thyroid cancer (Review)

Ma C, Xie J, Chen Q, Wang G, Zuo S

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[Intervention Review]

Amifostine for salivary glands in high-dose radioactive iodine treated differentiated thyroid cancer

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ABSTRACT

Background

Radioactive iodine treatment for differentiated thyroid cancer possibly results in xerostomia. Amifostine has been used to prevent the effects of irradiation to salivary glands. To date, the effects of amifostine on salivary glands in radioactive iodine treated differentiated thyroid cancer remain uncertain.

Objectives

To assess the effects of amifostine on salivary glands in high-dose radioactive iodine treated differentiated thyroid cancer.

Search methods

Studies were obtained from computerized searches of MEDLINE, EMBASE, *The Cochrane Library* and paper collections of conferences held in Chinese.

Selection criteria

Randomised controlled clinical trials and quasi-randomised controlled clinical trials comparing the effects of amifostine on salivary glands after radioactive iodine treatment for differentiated thyroid cancer with placebo and a duration of follow up of at least three months.

Data collection and analysis

Two authors independently assessed risk of bias and extracted data.

Main results

Two trials with 130 patients (67 and 63 patients randomised to intervention versus control) were included. Both studies had a low risk of bias. Amifostine versus placebo showed no statistically significant differences in the incidence of xerostomia (130 patients, two studies), the decrease of scintigraphically measured uptake of technetium-99m by salivary or submandibular glands at twelve months (80 patients, one study), and the reduction of blood pressure (130 patients, two studies). Two patients in one study collapsed after initiation of amifostine therapy and had to be treated by withdrawing the infusion and volume substitution. Both patients recovered without sequelae. Meta-analysis was not performed on the function of salivary glands measured by technetium-99m scintigraphy at three months after high dose radioactive iodine treatment due to the highly inconsistent findings across studies (I^2 statistic 99%). None of the included trials investigated death from any cause, morbidity, health-related quality of life or costs.

Authors' conclusions

Results from two randomised controlled clinical trials suggest that the amifostine has no significant radioprotective effects on salivary glands in high-dose radioactive iodine treated differentiated thyroid cancer patients. Moreover, no health-related quality of life and other patient-oriented outcomes were evaluated in the two included trials. Randomised controlled clinical trials with low risk of bias investigating patient-oriented outcomes are needed to guide treatment choice.

PLAIN LANGUAGE SUMMARY

Amifostine for salivary glands in high-dose radioactive iodine treated differentiated thyroid cancer

Thyroid cancer is the most common malignancy of the endocrine system consisting of several subtypes like papillary carcinoma (accounting for 80% of cases) and follicular carcinoma (accounting for 11% of cases). These are collectively referred to as 'differentiated thyroid cancer'. Treatment with radioactive iodine after surgery (ablation of the thyroid gland or 'thyroidectomy') is important for the detection of metastatic disease and for the destruction of the remaining thyroid tissue with microscopic cancer. After radioactive iodine treatment, adverse effects may happen in the salivary glands and cause salivary gland swelling and pain, usually involving the parotid. The symptoms may develop immediately after a therapeutic dose of radioactive iodine or months later and progress in intensity with time. Secondary complications reported include dry mouth ('xerostomia') and taste alterations.

Amifostine is thought to be a radioprotector of salivary glands used in conjunction with radioiodine therapy. This medication is administered intravenously and was reported to ameliorate the damage of salivary glands caused by radioactive iodine therapy.

We found only two randomised controlled trials in which the effects of amifostine were compared with placebo. The two randomised clinical trials investigated 130 patients treated with high dose radioactive iodine for thyroid cancer. Altogether data from the two trials suggest that amifostine has no obvious protective effects on the salivary glands in these patients. Two patients in one study collapsed after initiation of amifostine therapy and had to be treated by withdrawing the infusion and volume substitution. Both patients recovered without sequelae.

Until better data become available, the use of sour candy or lemon juice to increase salivation might be more appropriate during radioactive iodine treatment for patients with differentiated thyroid cancer. Patients should be well informed of the importance of hydration, acid stimulation and glandular massage after radioactive iodine treatment. In addition, early recognition and treatment of xerostomia may improve outcomes.

BACKGROUND

Description of the condition

Radioactive iodine for thyroid remnants and metastatic disease of differentiated thyroid carcinoma

Thyroid cancer is the most common endocrine malignancy (Edwards 2002; Wartofsky 2002) with the most frequent histologic subtype of thyroid carcinoma being papillary (accounting for 80% of cases) followed by follicular carcinoma (accounting for 11% of cases). These are commonly collectively referred to as differentiated thyroid cancer (Edwards 2002; Sawka 2004).

Radioactive iodine ablation of remnant thyroid tissue in patients with differentiated thyroid cancer who have undergone total or subtotal thyroidectomy is important for the detection of metastatic disease, and for the destruction of the remaining thyroid tissue with residual microscopic cancer (Fraker 1997; Zidan 2004). In many centres, the use of radioactive iodine has been established for the ablation of remnant thyroid tissue (Haugen 2006; Sawka 2004) and metastatic disease of differentiated thyroid carcinoma (Bohuslavizki 1999a; Schlumberger 1998) after patients had a thyroidectomy. A systematic review suggested that radioactive iodine ablation may be beneficial in decreasing recurrence of well-differentiated thyroid cancer (Sawka 2004). However, results are inconsistent both for some outcomes and the incremental benefit of remnant ablation in low-risk patients treated with bilateral thyroidectomy.

Irradiation effects of high dose radioactive iodine on salivary glands

In the management of thyroid remnants and metastatic disease of differentiated thyroid carcinoma, the sodium iodide symporter (NIS) plays an important role in radioactive iodine uptake. NIS is an integral plasma membrane glycoprotein which (as the crucial first step for thyroid hormone synthesis) mediates the active transport of the iodide ion into the thyroid follicular cells (Dai 1996; Levy 1998; Smanik 1996; Spitzweg 1998). NIS expression has also been demonstrated in many non thyroidal tissues, including salivary glands, lacrimal glands, gastric mucosa, lactating mammary glands, placenta and thymus (Chung 2002; Spitzweg 1999).

After radioactive iodine treatment, common side effects may include salivary gland swelling and pain, usually involving the parotid. The symptoms may develop immediately after a therapeutic dose of radioactive iodine or months later and progress in intensity with time. In conjunction with the radiation associated sialadenitis, secondary complications reported include xerostomia and taste alterations (Mandel 2003).

Apart from specific uptake by thyroid tissue, the ß-emitting radioactive iodine is accumulated actively by an adenosine triphosphate (ATP)-dependent sodium/potassium/chloride cotransport, i.e. the sodium iodide symporter in salivary glands due to its similar atomic diameter and its comparable electric charge (Albrecht 1976; Baum 1993; Helman 1987). Therefore, the salivary glands also have the capacity to concentrate iodide selectively. The principal site of the iodide transport into saliva is the epithelium of the parotid salivary glands' intralobular ducts (Gates 1967; Mishkin 1981). Radioiodine is extracted from periductal capillaries and concentrated by the ductal epithelium whereupon it is secreted into the duct lumen and transported into the oral cavity. The salivary concentration of radioiodine has been reported to vary from 20 to 100 times that found in the serum (Levenson 1994; Maier 1987; Myant 1960; Rigler 1955,). It has been calculated that up to 24% of the administered radioactive iodine dose for thyroid cancer therapy is lost in the saliva (Mandel 2003). In the process of concentrating the radioactive iodine, the salivary glands are exposed to the damaging effects of irradiation.

Although all salivary glands are involved in the transport of the radioactive iodine into the saliva, the parotid glands are most active and their serous cells are more susceptible than mucous acini to the deleterious effects of ionizing radiation. Therefore, the serous parotid gland will demonstrate a more intense radiation sialadenitis than the mixed mucous and serous cell-containing submandibular and sublingual salivary glands (Abramson 1969; Rigler 1955). Serous cells are particularly concerned with secretion of salts and zymogen, the precursor of amylase. The mucous cells secrete mucin, a lubricant that eases swallowing and acts as a protective oral mucosal barrier. The radioactive iodine irradiation of the salivary glands also causes endothelial damage to the glandular vasculature (Maier 1987). An increase in capillary permeability results in the leakage of plasma proteins and electrolytes into the surrounding interstitial tissues. The simultaneously injured irradiated intralobular ducts lose their ability to filter and prevent plasma proteins from entering the saliva. As a result of these two mechanisms, elevated protein levels are evident in parotid saliva (Deeg 1988; Maier 1987). Elevated sodium and chloride levels are also found in parotid saliva because a radiation-damaged duct does not have the normal duct's ability to resorb these electrolytes secreted by the terminal acinar cells as saliva progresses through the duct system. Furthermore, salivary phosphate levels are decreased when the damaged epithelium of the intralobular duct's wall fails in its normal function to transport phosphate into the saliva. Biochemical changes in saliva can be expected in all patients receiving therapeutic radioactive iodine (Levenson 1994; Maier 1987), the extent of which is dose dependent.

Another side effect of radioiodine treatment is damage of normal tissues in the radiation port, in particular the salivary glands (Mossman 1994), resulting in transient or long-lasting xerostomia (Bohuslavizk 1995; Bohuslavizki 1996; Bohuslavizki 1997). Therefore, radioiodine treatment is performed under salivary gland stimulation to decrease impairment of salivary gland function (Becker 1995; Clarke 1994; Spiegel 1986). However, even under salivary gland-stimulating conditions, parenchymal damage could be demonstrated after radioactive iodine treatment using quantitative salivary gland scintigraphy (Allweiss 1984; Bohuslavizki 1996; Bohuslavizki 1997; Bohuslavizki 1998a; Bohuslavizki 1998b).

Salivary gland scintigraphy and effects of amifostine on salivary glands

Salivary gland scintigraphy is a diagnostic test with high sensitivity, specificity, accuracy and positive and negative predictive values in detecting Sjögren's Syndrome (Dugonji 2008). The imaging technique is widely accepted as an objective assessment of salivary gland function and a diagnostic criterion of primary Sjögren's Syndrome (Vinagre 2008). Quantitative and semi-qualitative salivary gland scintigraphy performed in a standardized method as described (Bohuslavizk 1995) enables the quantitative evaluation of salivary glands' parenchymal function after radioactive iodine

treatment in the management of differentiated thyroid cancer. It is characterized by an excellent intraindividual observer variability, as well as by a good reproducibility allowing the detection of changes in parenchymal function in the range of as little as 5% to 10% (Bohuslavizki 1998a; Bohuslavizki 1998b). This enables both the early detection of the Sjögren's Syndrome (Bohuslavizk 1995) and parenchyma impairment of salivary glands following radioactive iodine therapy (Bohuslavizki 1998a; Bohuslavizki 1998b). Therefore, salivary gland scintigraphy proves to be a suitable imaging modality for quantitative evaluation of salivary gland parenchymal function.

Description of the intervention

Amifostine is a radioprotector of salivary glands used in conjunction with radioiodine therapy. After being administered intravenously, amifostine is rapidly cleared from plasma with an alpha half-life of less than one minute and a beta half-life of less than 10 minutes (Shaw 1988). Before radioactive iodine administration, doses of amifostine given ranged from 300 mg/m^2 (Kim 2008) to 500 mg/m^2 over 15 minutes (Bohuslavizki 1998b). It was reported that amifostine lessened the parenchymal damage of salivary glands induced by radioactive iodine therapy (Bohuslavizki 1998a; Bohuslavizki 1998b). This may improve quality of life of patients with differentiated thyroid cancer treated with radioactive iodine. However, a recent study did not show cytoprotective effects of amifostine for differentiated thyroid cancer patients treated with radioactive iodine (Kim 2008). As a result of contradictory evidence, it is necessary to establish the effect of amifostine for salivary glands in radioactive iodine treated differentiated thyroid cancer.

Adverse effects of the intervention

The most common adverse effects of amifostine are emesis, hypotension, somnolence, and sneezing (Boehme 2004; Bohuslavizki 1999b; Rades 2004). Less common side effects include a metallic taste, flushing, malaise, hypocalcaemia, chills, and idiosyncratic reactions such as fever and rash (Boehme 2004; Rades 2004). Consequently, careful inspections should be undertaken while intravenous administration of amifostine: First, blood pressure should be checked prior to the amifostine infusion and every minute during the infusion and up to 15 min afterwards. Secondly, amifostine infusion should be stopped if acute toxicity such as allergic reactions equal or greater than grade 2 (according to the common toxicity criteria) or vomiting and hypotension equal or greater than grade 3 occur (Rades 2004; Trotti 2000). Thirdly, due the emetic potency of amifostine, treatment with 40 mg dexamethasone and 5 mg tropisetron (Bohuslavizki 1998a; Bohuslavizki 1999b) or 8 mg ondansetron are administered before amifostine treatment (Kim 2008; Rades 2004). In order to reduce the risk of amifostine induced hypotension, patients irradiated for head and neck cancer receive an intravenous infusion of 1000 ml fluid (Rades 2004). Hypotension may be overcome by withdrawal of amifostine and volume substitution (Bohuslavizki 1999b). However, results from patients, irradiated for head and neck cancer, suggested an association with a high rate of serious adverse effects which resulted in the discontinuation of amifostine. The investigators concluded that the intravenous application of amifostine must be regarded as a treatment with a high toxicity potential, which has been underestimated until recently (Rades 2004). Alternatives of intravenous amifostine are considered. Subcutaneous application is reported to be less toxic than intravenous application. However, the rate of severe adverse effects was greater than 10% (Anne 2002; Koukourakis 2000).

How the intervention might work

Amifostine is an organic thiophosphate that is dephosphorylated in normal tissues to its active metabolite, WR-1065 (Cappizi 1999). Amifostine was originally developed as a radioprotective agent within the Anti-Radiation Drug Development Program initiated by the United States Army at the Walter Reed Army Institute of Research (Washington D. C) in the early 1950s (Patt 1949). Since numerous preclinical studies in cell cultures and animal models showed that, following dephosphorylation to its active metabolite WR-1065, amifostine selectively protected normal tissue from damaging effects of irradiation (Menard 1984; Phillips 1973; Pratt 1980; Sodicoff 1978a; Sodicoff 1978b; Washburn 1978; Yuhas 1980), several clinical studies were initiated, confirming its radioprotective potency (McDonald 1994; Niibe 1985; Takahashi 1986). This resulted in an approval of amifostine in Germany, in 1995, for the supportive therapy of patients with ovarian cancer being treated with cisplatin derivatives in order to minimize the myelotoxic side effects of cisplatin.

The mechanism of radioprotective effects on normal tissue as compared to tumour tissue by amifostine, is suggested to be caused by two effects. First, amifostine is accumulated much more in normal tissue as compared to malignant transformed cells (Rasey 1985; Rasey 1986b; Utley 1976a; Yuhas 1980). Secondly, the alkaline phosphatase necessary for dephosphorylation of amifostine to its active compound WR-1065 is more effective in the alkaline environment of normal tissue than in the acidic tumour tissues (Utley 1976b). Once activated inside the cell, WR-1065 acts as a scavenger of oxygen free radicals. Since amifostine is known to be accumulated extensively in salivary glands (Phillips 1973; Rasey 1985; Rasey 1986a; Rasey 1988; Utley 1976b; Utley 1981; Washburn 1974; Yuhas 1980), it seemed reasonable to use amifostine as a radioprotector in patients with head and neck tumours receiving external radiation therapy. Some studies have been undertaken in head and neck tumours yielding promising results concerning the reduction of radiation-induced salivary gland damage (McDonald 1994; Niibe 1985; Takahashi 1986). Since radiation effects of external radiation and radioiodine therapy are in general caused by the same mechanisms, i.e. the production of free radicals, it seemed promising to use this radioprotection of salivary glands by amifostine in high-dose radioiodine therapy.

Why it is important to do this review

The most frequent non-thyroidal complication of radioiodine therapy for differentiated thyroid cancer is salivary gland dysfunction, which may be transient or permanent. Since differentiated thyroid cancer has a good prognosis, reduction of long-term side effects is important. Even after using salivary gland acid stimulating agents, parenchymal damage could be demonstrated, following high-dose radioiodine treatment, using quantitative salivary gland scintigraphy (Allweiss 1984; Bohuslavizki 1996; Bohuslavizki 1997; Bohuslavizki 1998a; Bohuslavizki 1998b). Amifostine is a potent radioprotector of salivary glands in radioiodine therapy. As a result, it has been reported that the parenchymal damage in salivary glands induced by high-dose radioiodine therapy can be reduced significantly by amifostine. This may improve quality of life of patients with differentiated thyroid cancer treated with radioactive iodine. Up

to now, the impact of amifostine for salivary glands in radioactive iodine treated differentiated thyroid cancer is controversial as no cytoprotective effect of amifostine has been found for these patients.

Currently, there are no systematic reviews of studies of amifostine for salivary glands in radioactive iodine treated differentiated thyroid cancer.

OBJECTIVES

To assess the effects of amifostine on salivary glands in high-dose radioactive iodine treated differentiated thyroid cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials and quasi-randomised controlled clinical trials.

Types of participants

Patients of any age or sex who have differentiated thyroid carcinoma after total or near -total thyroidectomy followed by radioactive iodine and amifostine treatment were included.

Patients with initial salivary gland dysfunction, connective tissue disease, or other conditions causing salivary gland dysfunction were excluded.

The diagnosis of differentiated thyroid carcinoma had to be established according to the definite pathohistological evaluation of the surgical specimen. Salivary gland dysfunction had to be established by means of questionnaires for symptoms or through salivary gland scintigraphy.

Types of interventions

Intervention

Amifostine treatment.

Control

Placebo or gland acid stimulating agents.

Types of outcome measures

Primary outcomes

- xerostomia (dry mouth);
- health-related quality of life.

Secondary outcomes

- death from any cause;
- morbidity;
- adverse effects;
- costs;
- salivary functions, measured by ^{99m}Tc-pertechnetate scintigraphy.

Covariates, effect modifiers and confounders

- age;
- gender;
- dose of radioactive iodine.

Timing of outcome measurement

The follow up had to be at least three months after administration of amifostine and radioactive iodine.

Search methods for identification of studies

Electronic searches

We used the following sources for the identification of trials:

- *The Cochrane Library* (issue 2, 2009);
- MEDLINE (until April 2009);
- EMBASE (until 2009).

We also searched databases of ongoing trials: 'Current Controlled Trials' (www.controlled-trials.com - with links to other databases of ongoing trials). For detailed search strategies please see Appendix 1.

Additional key words of relevance could have been detected during any of the electronic or other searches. If this was the case, electronic search strategies would have been modified to incorporate these terms. Studies published in any language were included.

Searching other resources

We tried to identify additional studies by searching the reference lists of included trials and (systematic) reviews, meta-analyses and health technology assessment reports noticed.

Data collection and analysis

Selection of studies

To determine the studies to be assessed further, two authors (MC and XJW) independently scanned the abstract, title or both sections of every record retrieved. All potentially relevant articles were investigated as full text. Interrater agreement for study selection was measured using the kappa statistic (Cohen 1960). Differences were marked and if these studies were included, the influence of the primary choice was planned to be subjected to a sensitivity analysis. Where differences in opinion existed, they were resolved by a third party. If resolving disagreement was not possible, the article was added to those 'awaiting assessment' and authors were contacted for clarification. An adapted QUOROM (quality of reporting of meta-analyses) flow-chart of study selection is attached (Moher 1999).

Data extraction and management

For studies that fulfilled inclusion criteria, two authors (MC and XJW) independently abstracted relevant population and intervention characteristics using standard data extraction templates (for details see 'Characteristics of included studies' and Table 1, Appendix 2 with any disagreements to be resolved by discussion, or if required by a third party. Any relevant missing information on the trial was planned to be sought from the original author(s) of the article, if required.

Assessment of risk of bias in included studies

Two authors (MC and XJW) assessed each trial independently. Possible disagreement were resolved by consensus, or with consultation of a third party in case of disagreement. We explored the influence of individual bias criteria in a sensitivity analysis (see under 'sensitivity analyses') using the Cochrane Collaboration's risk of bias tool. Interrater agreement for key bias indicators (e.g. allocation concealment, incomplete outcome data) were calculated using the kappa statistic (Cohen 1960). In cases of disagreement, the rest of the group was consulted and a judgement was made based on consensus.

Measures of treatment effect

Dichotomous data

For dichotomous data (for example, patients experiencing sialoadenitis, hypogeusia or taste loss, dry mouth with or without repeated sialadenitis, the incidence of radiation induced salivary gland neoplasms and other adverse effects), the number of participants experiencing the event and the total number of participants in each arm of the trial were extracted. Relative risks were used.

Continuous data

For continuous data (for example, maximal secretion, uptake and uptake time of ^{99m}Tc pertechnetate in parotid and submandibular glands), we extracted the arithmetic means and standard deviations for each group. Mean differences were used.

Unit of analysis issues

Special issues in the analysis of studies with non-standard designs, such as cluster-randomised trials, were planned to be described.

Dealing with missing data

Relevant missing data were planned to obtain from authors, if feasible. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat (ITT) and per-protocol (PP) population was carefully performed. Attrition rates, for example drop-outs, losses to follow up and withdrawals were investigated. Issues of missing data and techniques to handle these (for example, last-observation-carried-forward (LOCF)) were critically appraised.

Dealing with duplicate publications

In the case of duplicate publications and companion papers of a primary study, we tried to maximise yield of information by simultaneous evaluation of all available data. In cases of doubt, the original publication (usually the oldest version) obtained priority.

Assessment of heterogeneity

In the event of substantial clinical, methodological or statistical heterogeneity, study results were not combined by means of meta-analysis. Heterogeneity was identified by visual inspection of the forest plots, by using a standard χ^2-test and a significance level of $\alpha = 0.1$, in view of the low power of such tests. Heterogeneity was specifically examined with I^2 (Higgins 2002), where I^2 values of 50% and more indicate a substantial level of heterogeneity (Higgins 2003). When heterogeneity was found, we attempted to determine potential reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

Funnel plots were planned to be used to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot (Sterne 2001). Therefore, we planned to carefully interpret results (Lau 2006).

Data synthesis

Data were summarised statistically if they were available, sufficiently similar and of sufficient quality. Statistical analysis was performed according to the statistical guidelines referenced in the newest version of the *Cochrane Handbook for Systematic Reviews of Interventions (* Higgins 2008).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned to be mainly performed if one of the primary outcome parameters demonstrated statistically significant differences between intervention and control groups. In any other case subgroup analyses would have been clearly marked as a hypothesis generating exercise.

The following subgroup analyses were planned:

- age;
- gender;
- dose of radioactive iodine.

Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- repeating the analysis excluding unpublished studies;
- repeating the analysis taking account of risk of bias, as specified above;
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results;
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

The robustness of the results was also planned to be tested by repeating the analysis using different measures of effects size (relative risk, odds ratio etc.) and different statistical models (fixed- and random-effects models).

RESULTS

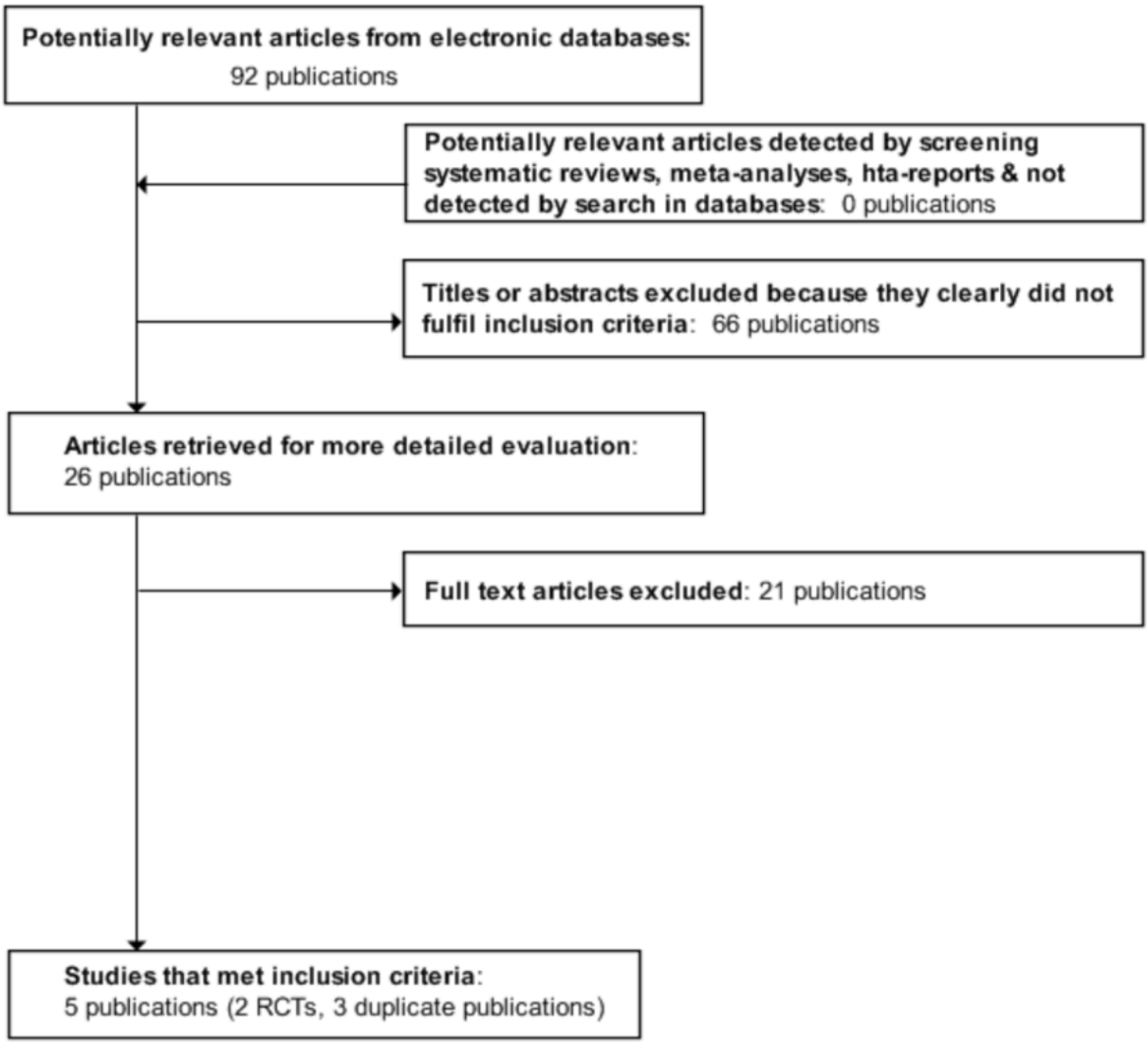
Description of studies

Results of the search

The electronic searches and hand searches revealed 92 studies. Of these references, we excluded 66 citations based on their title, abstract or both because they were not relevant to the question under study. After reading the full text of 26 potentially relevant publications, 21studies were excluded because they did not fulfil the inclusion criteria, five potential controlled clinical trials were retrieved for further assessment. Two randomised controlled clinical trials (Bohuslavizki 1998b; Kim 2008) were included. Trial durations were from 2004 to 2006 in one trial (Kim 2008), but not mentioned in the other (Bohuslavizki 1998b). Summary details of these trials are given in the 'Characteristics of

included studies' section. Three seemingly duplicate studies were excluded (Bohuslavizki 1998a; Bohuslavizki 1999a; Bohuslavizki 1999b). For an overview (Figure 1), please see the adapted QUOROM (quality of reporting of meta-analyses) flow-chart of study selection (Moher 1999).

Figure 1. Adapted QUOROM (quality of reporting of meta-analyses) flow-chart of study selection



Dealing with duplicate publications

Four controlled clinical trials by the same author were published in 1998 and 1999. We included the original publication (the oldest version).

Included studies

Altogether 130 patients with differentiated thyroid cancer participated in two trials. Fifty participants in Germany (Bohuslavizki 1998b) and 80 participants in the Republic of Korea were recruited ranging in age from 19 to 81 years. The diagnosis of xerostomia was established according to the World Health Organization (WHO) criteria in one trial (Bohuslavizki 1998b), and by a xerostomia questionnaire for symptoms assessment in another trial (Kim 2008). No inclusion or exclusion criteria were described in the two trials (Bohuslavizki 1998b; Kim 2008). Neither trial described disease duration. According to the results mentioned in the two included trials, there were no losses to follow up. Co-medications such as antiemetic treatment with 40 mg dexamethasone and 5 mg tropisetron were used in one trial (Bohuslavizki 1998b), and 8 mg ondansetron in the other trial (Kim 2008). Co-morbidities were not mentioned.

Excluded studies

Three potential trials being duplicate publications by the same author were excluded (Bohuslavizki 1998a; Bohuslavizki 1999a; Bohuslavizki 1999b).

Risk of bias in included studies

Two randomised controlled clinical trials were included. The risk of bias of the included trials was considered as low. No patients were lost to follow up. Details of the studies are listed in the Characteristics of included studies and Risk of bias in included studies tables.

Allocation

Allocation concealment was not mentioned in the included studies.

Blinding

One trial reported blinding (Bohuslavizki 1998b).

Incomplete outcome data

Outcome data were available for all randomised patients.

Selective reporting

None detected.

Other potential sources of bias

Summary data on age, gender, tumour pathology and staging were reported for all participants. No significant differences were found between comparison groups at baseline.

Effects of interventions

Primary outcomes

Amifostine versus placebo showed no significant differences in the incidence of xerostomia ((dry mouth and hypogeusia): 130 patients, two trials, Analysis 1.1.

No study analysed health-related quality of life.

Secondary outcomes

No study investigated death from any cause, morbidity or economic outcomes.

There were no significant differences in salivary functions, measured by ^{99m}Tc-pertechnetate scintigraphy (80 patients, one trial, Analysis 2.1, Analysis 2.2).

Meta-analysis was not performed on the decreased uptake of ^{99m}Tc-pertechnetate in scintigraphy by parotid and submandibular glands at three months due to the highly inconsistent findings across studies (I^2 = 99%).

Adverse effects other than incidence of xerostomia

There were no significant differences in reduction of blood pressure (130 patients, two trials, Analysis 1.2). However, two patients in one trial collapsed during amifostine infusion due to a drop in systolic/diastolic blood pressure from 170/80 mm Hg to 130/60 mm Hg and 180/82 mm Hg to 145/75 mm Hg, respectively. This adverse effect was treated by withdrawing the infusion and volume substitution. Both patients recovered without sequelae (Bohuslavizki 1998b). Fur full details of adverse events, see Appendix 2.

Compliance

Amifostine treatment was taken for a short term only. Compliance appeared satisfactorily in the two trials.

Subgroup analyses

Not possible for age and gender due to low number of studies.

In one trial, radioactive doses of 3 GBq versus 6 GBq (25 patients, one trial, Analysis 3.1, Analysis 3.2) showed no significant differences of salivary glands' function at three months in patients treated with amifostine (Bohuslavizki 1998b).

Sensitivity analyses

Not possible due to low number of studies.

DISCUSSION

Summary of main results

Two randomised controlled clinical trials involving 130 patients were included. All of them had a low risk of bias.

No significant benefits of amifostine therapy were found for the salivary glands in high-dose radioactive iodine treated differentiated thyroid cancer patients in terms of incidence of xerostomia (dry mouth and hypogeusia). Amifostine versus placebo showed no significant differences in adverse effects like reduction of systolic blood pressure and salivary functions as measured by ^{99m}Tc-pertechnetate scintigraphy.

The very wide confidence intervals for both xerostomia and adverse effects may be due to the different durations of follow up, three months (Bohuslavizki 1998b), and 12 months (Kim 2008), respectively. Furthermore, no inclusion or exclusion criteria were reported in the two included studies, patients with salivary gland dysfunction, connective tissue disease, or other conditions causing salivary gland dysfunction should be excluded in these trials. Different doses of amifostine were used with 500 mg/m^2 in one trial (Bohuslavizki 1998b) and 300 mg/m^2 amifostine in the other study (Kim 2008), which may also lead to different therapeutic effects. None of the included trials evaluated death from any cause, morbidity, health-related quality of life or costs.

Overall completeness and applicability of evidence

The two included randomised controlled clinical trials, in which age, gender, tumour pathology and tumour staging were similar at baseline, had similar overall low risk of bias. There were no withdrawals nor losses to follow up in the two trials. The diagnosis of xerostomia was established according to the World Health Organization (WHO) criteria in one trial (Bohuslavizki 1998b), and a xerostomia questionnaire for symptoms assessment in another trial (Kim 2008). No inclusion or exclusion criteria were reported in the two included studies. Dry mouth is a common disorder in elderly individuals (Narhi 1994) and xerostomia related symptoms should be assessed before radioactive iodine treatment for patients with differentiated thyroid cancer. Patients with dry month or a systemic autoimmune disorder should be excluded in these trials. Therefore, amifostine cannot currently be recommended for patients with radioactive iodine treated differentiated thyroid cancer.

Radioactive iodine doses of equal or less than 3 or greater than 6 GBq (Bohuslavizki 1998b) and 3.75 to 7.5 GBq (Kim 2008) were used in the included trials. In a subgroup analysis on the effects of radioactive iodine doses on salivary glands function, Bohuslavizki et al reported no significant differences of 3 GBq versus 6 GBq

doses (Bohuslavizki 1998b). The other included study did not show an association between higher radioactive iodine doses and the development of xerostomia (Kim 2008).

Quality of the evidence

Only two trials with low risk of bias but generally inadequately reported investigated 130 participants. There was no information about patient-oriented endpoints like death from any cause, morbidity, health-related quality of life or economic outcomes. Calculation of sample size was not reported in any trial. No inclusion or exclusion criteria were reported in both included studies. Different doses of amifostine were used with 500 mg/m^2 in one trial (Bohuslavizki 1998b) and 300 mg/m^2 amifostine in the other trial (Kim 2008), which may lead to different therapeutic effects. A follow up at three and 12 months in the two trials does not appear to be long enough to evaluate potential irradiation induced damage on salivary function. Different calculations of scintigraphically detected technetium-99m (^{99m}Tc-pertechnetate) uptake by salivary glands were used in the two trials (Bohuslavizki 1998b; Kim 2008). Because of the described heterogeneity, we did not calculate pooled effect sizes in meta-analyses.

Moreover, outcome assessment could have been blinded but the trials did not report this blinding method. This could have resulted in exaggerated or minimized effects of the intervention.

Potential biases in the review process

None known.

Agreements and disagreements with other studies or reviews

Xerostomia characterized by hypogeusia and dry mouth is one of the adverse effects of radioactive iodine treatment for differentiated thyroid cancer. Xerostomia causes significant oropharyngeal disorders, pain and an impaired quality of life (Loesche 1995). It seems possible that the greater the dose of radioactive iodine, the higher the possibility of xerostomia (Bohuslavizki 1998b; Kim 2008). A higher radioactive iodine (greater than 6 GBq) dose showed significantly decreased technetium-99m uptake in the parotid and submandibular glands in patients without amifostine treatment (Bohuslavizki 1998b). This was confirmed by another study (Kim 2008), so the dose of radioactive iodine had significant effects on the salivary gland function in patients with differentiated thyroid cancer. Similar to the results in this review, sixty per cent of distorted taste in patients treated with a dose of 4 GBq radioactive iodine has been reported. Twenty-seven per cent hypogeusia were found in patents treated with a dose of 5.5 GBq radioactive iodine (Brown 1984). However, 3 GBq vs 6 GBq radioactive iodine (subgroup analysis) doses had no significant effects on salivary glands in 25 patients treated with amifostine, which indicates that amifostine may have protective effects on salivary glands in patients treated with higher dose radioactive iodine (Bohuslavizki 1998b).

It has not been proven whether or not amifostine influences the therapeutic efficacy of radioactive iodine in the treatment of differentiated thyroid cancer (Mandel 2003). Due to the limited results from the two included trials (Bohuslavizki 1998b; Kim 2008), the use of sour candy (Freitas 1985; Mazzaferri 2000) or lemon juice (Spiegel 1985) to increase salivation might be more appropriate during radioactive iodine treatment for patients with differentiated thyroid cancer. Patients should be well informed of the importance of hydration, acid stimulation and glandular massage after radioactive iodine treatment. In addition, early recognition and treatment of xerostomia serves to lessen patient morbidity (Mandel 2003).

AUTHORS' CONCLUSIONS

Implications for practice

There is no good evidence from well-designed trials for or against amifostine therapy for salivary glands in high-dose radioactive iodine treated differentiated thyroid cancer. However, our findings suggest that amifostine has no significant radioprotective effects on salivary glands in this patient cohort.

Implications for research

Randomised controlled clinical trials with low risk of bias are required to evaluate amifostine for salivary glands in high dose radioactive iodine treated differentiated thyroid cancer. The effects of amifostine should be evaluated and compared in the same dose for these patients. Patients with systemic autoimmune disorders should be excluded. Outcome measures should include health-related quality of life, morbidity, death from any cause and costs, adverse events and the effects of radioactive iodine doses on salivary glands. The salivary function should be dynamically surveyed in the longer term and in the same way. The diagnosis of xerostomia should be based on the same diagnostic criteria.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bohuslavizki 1998b

Methods	RANDOMISED CONTROLLED CLINICAL TRIAL (RCT): yes RANDOMISATION RATIO: 1:1

Bohuslavizki 1998b *(Continued)*

	NON-INFERIORITY DESIGN: no EQUIVALENCE DESIGN: no PARALLEL / CROSSOVER / FACTORIAL RCT: PARALLEL RCT CONTROLLED CLINICAL TRIAL (CCT): no.
Participants	WHO PARTCIPATED: Patients (M/F = 19/31) aged between 19 and 81 years, with differentiated thyroid cancer. 25 participants were on intervention, 25 participants were on control. INCLUSION CRITERIA: not reported. EXCLUSION CRITERIA: not reported. DIAGNOSTIC CRITERIA: Pathologically established differentiated thyroid cancer, World Health Organization (WHO) criteria for xerostomia. CO-MORBIDITIES: not reported. CO-MEDICATIONS: not reported.
Interventions	NUMBER OF STUDY CENTRES: Two centres. COUNTRY/ LOCATION: Germany. SETTING: In-patients. INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Intervention: intravenous, 500 mg/m^2 amifostine. Control: physiologic saline solution. TREATMENT BEFORE STUDY: 40 mg dexamethasone and 5 mg tropisetron as an antiemetic treatment. TITRATION PERIOD: not applicable.
Outcomes	PRIMARY OUTCOME(S): The outcomes were evaluated by salivary function, on the basis of principal symptoms, signs and salivary gland imaging after three months an one year, respectively. 1. Dry mouth hypogeusia 2. Total effectiveness rate SECONDARY OUTCOMES: 1. Adverse effects 2. Uptake decrease of Tc-99m-pertechnetate in parotid and submandibular glands (three months). ADDITIONAL OUTCOMES: Subgroup analysis: radioactive doses 3 GBq vs 6 GBq uptake on salivary glands function.
Study details	DURATION OF INTERVENTION: Intervention: 25 participants received 500 mg/m2 amifostine intravenously. Control: 25 participants received physiologic saline solution before high-dose radioactive iodine treatment. DURATION OF FOLLOW-UP: 3,12 months. RUN-IN PERIOD: not reported.
Publication details	LANGUAGE OF PUBLICATION: English.

Bohuslavizki 1998b *(Continued)*

	COMMERCIAL FUNDING: no NON-COMMERCIAL FUNDING: yes PUBLICATION STATUS (PEER REVIEW JOURNAL): yes PUBLICATION STATUS (JOURNAL SUPPLEMENT): no PUBLICATION STATUS (ABSTRACT): no
Stated aim of study	"to examine prospectively the effects of amifostine in differentiated thyroid cancer patients following high-dose radioiodine treatment"
Notes	./.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "Patients were assigned randomly either to the placebo group or to the treatment group, which received 500 mg/m^2 amifostine".
Allocation concealment?	Unclear risk	Not mentioned.
Blinding? All outcomes	Low risk	Quote: "double-blind".
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data are available for all included patients.
Free of selective reporting?	Low risk	All included patients were reported.
Free of other bias?	Low risk	None detected.

Kim 2008

Methods	RANDOMISED CONTROLLED CLINICAL TRIAL (RCT): yes RANDOMISATION RATIO: 1:1 NON-INFERIORITY DESIGN: no EQUIVALENCE DESIGN: no PARALLEL / CROSSOVER / FACTORIAL RCT: PARALLEL RCT CONTROLLED CLINICAL TRIAL (CCT): no
Participants	WHO PARTCIPATED: Patients(M/F = 9/71) aged between 21 and 58 years, with differentiated thyroid cancer. 42 participants were on intervention, 38 participants were on control. INCLUSION CRITERIA: not reported. EXCLUSION CRITERIA: not reported. DIAGNOSTIC CRITERIA:

Kim 2008 *(Continued)*

	Pathologically established well differentiated thyroid cancer, xerostomia symptoms were self-assessed by means of a detailed questionnaire covering the symptoms of dry mouth (dryness, dental deterioration, gingivitis, infections, parotitis, lack of taste, and difficulty swallowing dry foods) and dry eyes (dryness, photosensitivity, sticking, burning, heaviness, redness, and eye infection). CO-MORBIDITIES: not reported. CO-MEDICATIONS: not reported.
Interventions	NUMBER OF STUDY CENTRES: Single centres. COUNTRY/ LOCATION: Republic of Korea. SETTING: In-patients. INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Intervention: intravenous, 300 mg/m^2 amifostine. Control: placebo. TREATMENT BEFORE STUDY: 8mg ondansetron one hour before radioactive iodine administration and every 8 hours after radioactive iodine application as an antiemetic treatment. TITRATION PERIOD: not applicable.
Outcomes	PRIMARY OUTCOME(S): The outcomes were evaluated by salivary function, on the basis of principal symptoms, signs and salivary gland imaging after 3,12 months, respectively. 1. Dry mouth and hypogeusia 2. Total effectiveness rate. SECONDARY OUTCOMES: 1. Adverse effects 2. Uptake decrease of Tc-99m-pertechnetate in parotid and submandibular glands (3 months)
Study details	DURATION OF INTERVENTION: Intervention: 42 patients received 300 mg/m^2 amifostine intravenously. Control: 38 patients received placebo. DURATION OF FOLLOW-UP: 3,12 months. RUN-IN PERIOD: not reported.
Publication details	LANGUAGE OF PUBLICATION: English. COMMERCIAL FUNDING: no NON-COMMERCIAL FUNDING: yes PUBLICATION STATUS (PEER REVIEW JOURNAL): yes PUBLICATION STATUS (JOURNAL SUPPLEMENT): no PUBLICATION STATUS (ABSTRACT): no
Stated aim of study	"to investigate with serial quantitative analysis of salivary gland scans the cytoprotective effect of amifostine on salivary glands in 131I-treated DTC patients"
Notes	./.

Kim 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "forty-two patients were assigned randomly to the amifostine treatment group".
Allocation concealment?	Unclear risk	Not mentioned.
Blinding? All outcomes	Low risk	Quote: "double-blind".
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data were available for all included patients.
Free of selective reporting?	Low risk	All included patients were reported.
Free of other bias?	Low risk	None detected.

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

Study	Reason for exclusion
Bohuslavizki 1998a	duplicate publication
Bohuslavizki 1999a	duplicate publication
Bohuslavizki 1999b	duplicate publication

DATA AND ANALYSES

Comparison 1. Adverse events

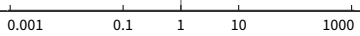
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of xerostomia (dry mouth and hypogeusia)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Reduction of blood pressure	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Adverse events, Outcome 1 Incidence of xerostomia (dry mouth and hypogeusia).

Study or subgroup	Amifostine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bohuslavizki 1998b	0/25	11/25		0%	0.04[0,0.7]
Kim 2008	21/42	21/38		0%	0.9[0.6,1.37]

Analysis 1.2. Comparison 1 Adverse events, Outcome 2 Reduction of blood pressure.

Study or subgroup	Amifostine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bohuslavizki 1998b	2/25	0/25		0%	5[0.25,99.16]
Kim 2008	0/40	0/40			Not estimable

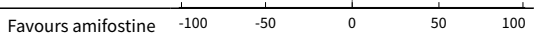


Comparison 2. Decrease in uptake of technetium-99m by parotid gland at 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Decrease in uptake of technetium-99m by parotid gland at 12 m	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Decrease in uptake of technetium-99m by mandibular gland at 12 m	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

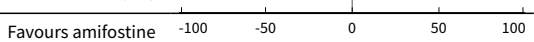
Analysis 2.1. Comparison 2 Decrease in uptake of technetium-99m by parotid gland at 12 months, Outcome 1 Decrease in uptake of technetium-99m by parotid gland at 12 m.

Study or subgroup	Amifostine N	Amifostine Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Kim 2008	42	11 (5.6)	38	10.7 (6.1)		0.3[-2.28,2.88]



Analysis 2.2. Comparison 2 Decrease in uptake of technetium-99m by parotid gland at 12 months, Outcome 2 Decrease in uptake of technetium-99m by mandibular gland at 12 m.

Study or subgroup	Amifostine N	Amifostine Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Kim 2008	42	14.2 (7.7)	38	12.3 (7.6)		1.9[-1.46,5.26]

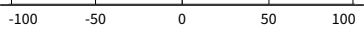


Comparison 3. Radioactive iodine dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Decrease in uptake of technetium-99m by parotid gland at 3 m	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Decrease in uptake of technetium-99m by submandibular glands at 3 m	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Radioactive iodine dose, Outcome 1 Decrease in uptake of technetium-99m by parotid gland at 3 m.

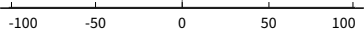
Study or subgroup	3 GBq		6 GBq		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Bohuslavizki 1998b	11	1 (6.1)	14	0.3 (4.3)		0.7[-3.55,4.95]



Favours 3 GBq Favours 6 GBq

Analysis 3.2. Comparison 3 Radioactive iodine dose, Outcome 2 Decrease in uptake of technetium-99m by submandibular glands at 3 m.

Study or subgroup	3 GBq		6 GBq		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Bohuslavizki 1998b	11	0.8 (5.2)	14	-0.6 (4.9)		1.4[-2.6,5.4]



Favours 3 GBq Favours 6 GBq

ADDITIONAL TABLES

Table 1. Study populations data

study ID	intervention	[n] screened	[n] randomised	[n] safety	[n] ITT	[n] finishing study	comments
Bohuslavizki 1998b	amifostine (I) placebo (C)	I: 25 C: 25 Total: 50	I: 25 C: 25 Total: 50	I: 25 C: 25 Total: 50	I: not mentioned C: not mentioned	I: 25 C: 25 Total: 50	none
Kim 2008	amifostine (I) placebo (C)	I: 42 C: 38 Total: 80	I: 42 C: 38 Total: 80	I: 42 C: 38 Total: 80	I: not mentioned C: not mentioned	I: 42 C: 38 Total: 80	none

ITT: intention-to-treat

APPENDICES

Appendix 1. Search strategies

Search terms

Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) = to substitute for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent.

MEDLINE (Ovid interface):

1.exp Amifostine/

2.(amifostin$ or ethyol$).ab,ti,ot.

3.exp Cytoprotection/

4.((cyto or radio or chemo) adj6 protect$).ab,ti,ot.

5. or/1-4

6.exp Thyroid Neoplasms/

7.(thyroid$ and (cancer or tumo?r$ or neoplasm$)).ab,ti,ot.

8.exp Salivary glands/
9. (salivary adj6 gland$).ab,ti,ot.

10.or/6-9

11.randomized controlled trial.pt.

12.controlled clinical trial.pt.

13. randomized.ab.

14.placebo.ab.

15.drug therapy.fs.

16. randomly.ab.

17.trial.ab.

18.groups.ab.

19.or/11-18

20.Meta-analysis.pt.

21.exp Review/

22.exp Technology Assessment, Biomedical/

23.exp Meta-analysis/

24.exp Meta-analysis as topic/

25.hta.tw,ot.

26. (health technology adj6 assessment$).tw,ot.

27.(meta analy$ or metaanaly$ or meta?analy$).tw,ot.

(Continued)

28. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or chochrane or cinhal or psychinfo or psychlit or healthstar or biosis or current content$ or systemat$)).tw,ot.

29.or/20-28

30.19 or 29

31.5 and 10 and 30

32.limit 31 to animals

33.limit 31 to humans

34.32 not 33

35.31 not 34

EMBASE:

1. exp Amifostine/

2. (amifostin$ or ethyol$).ab,ti.

3. exp Cell protection/

4.((cyto or radio or chemo) adj6 protect$).ab,ti.

5.or/1-4

6.exp Thyroid Tumor/

7.(thyroid$ and (cancer or tumo?r$ or neoplasm$ or carcinom$)).ab,ti.

8. exp Salivary Gland/

9.(salivary adj6 gland$).ab,ti.

10.or/6-9

11.random$.tw.

12.(crossover$ or cross over$).tw.

13.placebo$.tw.

14.(double adj blind$).tw.

15.(single adj blind$).tw.

16.(assign$ or allocat$ or volunteer$).tw.

17.Crossover Procedure/

18.Double Blind Procedure/

19.Randomized Controlled Trial/

20.Controlled Clinical Trial/

21.Single Blind Procedure/

22.Randomization/

23.or/11-22

(Continued)

24.exp meta analysis/

25.exp Review/

26.(metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.

27.((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinhal or psychinfo or psychlit or healthstar or biosis or current content$ or systematic$)).ab,ti,ot.

28.exp Literature/

29.exp Biomedical Technology Assessment/

30.hta.tw,ot.

31.(health technology adj6 assessment$).tw,ot.

32.or/24-31

33.23 or 32

34.5 and 10 and 33

35.limit 34 to animal

36.limit 34 to human

37.35 not 36

38.34 not 37

The Cochrane Library **:**

#1 MeSH descriptor Amifostine explode all trees

#2 (amifostin* or ethyol*)

#3 MeSH descriptor Cytoprotection explode all trees

#4 ((cyto or radio or chemo) near6 protect*)

#5 (#1 OR #2 OR #3 OR #4)

#6 MeSH descriptor Thyroid Neoplasms explode all trees

#7 MeSH descriptor Salivary Glands explode all trees

#8 (thyroid* and (cancer or carcinom* or tumo?r* or neoplasm*))

#9 (salivary near6 gland*)

#10 (#6 OR #7 OR #8 OR #9)

#11 (#5 AND #10)

Appendix 2. Adverse events

Characteristic	Bohuslavizki 1998b	Kim 2008
Intervention (I)	amifostine (I)	amifostine (I)
Control (C)	placebo (C)	placebo (C)

(Continued)

Deceased participants [n/N]	I: 0 / 25 C: 0 / 25 Total: 0 / 50	I: 0 / 42 C: 0 / 38 Total: 0 / 80
Adverse events [n / %]	I: 2 / 8 C: 0 / 0 Total: 2 / 4	I: 0 / 0 C: 0 / 0 Total: 0 / 0
Serious adverse events [n / %]	I: 2 / 8 C: 0 / 0 Total: 2 / 4	I: 0 / 0 C: 0 / 0 Total: 0 / 0
Drop-outs due to adverse events [n / %]	I: 0 / 0 C: 0 / 0 Total: 0 / 0	I: 0 / 0 C: 0 / 0 Total: 0 / 0
Hospitalisation [n / %]	I: 2 / 8 C: 0 / 0 Total: 2 / 4	I: 0 / 0 C: 0 / 0 Total: 0 / 0
Out-patient treatment [n / %]	I: 0 / 0 C: 0 / 0 Total: 0 / 0	I: 0 / 0 C: 0 / 0 Total: 0 / 0
Symptoms [n / %]	I: 2 / 8 C: 0 / 0 Total: 2 / 4	I: 0 / 0 C: 0 / 0 Total: 0 / 0

Footnotes:

CONTRIBUTIONS OF AUTHORS

MA CHAO: Drafting and co-drafting of the protocol/review, data selection and analysis.

XIE JIAWEI: Drafting and co-drafting of the protocol/review.

CHEN QINGFENG: Searching, selection of studies.

WANG GUOMING: Assistance with data selection.

ZUO SHUYAO: Searching, selection of studies.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- West China Hospital Evidence Based Center, China.

External sources

- West China Hospital Evidence Based Center, China.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

No.

INDEX TERMS

Medical Subject Headings (MeSH)

Adenocarcinoma, Follicular; Amifostine [*therapeutic use]; Carcinoma, Papillary [radiotherapy]; Iodine Radioisotopes [*adverse effects]; Radiation Injuries [diagnostic imaging] [*prevention & control]; Radiation-Protective Agents [*therapeutic use]; Radionuclide Imaging; Randomized Controlled Trials as Topic; Salivary Glands [diagnostic imaging] [*drug effects] [radiation effects]; Thyroid Neoplasms [*radiotherapy]; Xerostomia [prevention & control]

MeSH check words

Humans