The effectiveness of commonly used mouthwashes for the prevention of chemotherapy-induced oral mucositis: a systematic review

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Daily chlorhexidine mouthwash is often recommended for preventing chemotherapy-induced oral mucositis. Povidone-iodine, NaCl 0.9%, water salt soda solution and chamomile mouthwash are also recommended. However, the effectiveness of these mouthwashes is unclear. Therefore, we performed a systematic review to assess the effectiveness of mouthwashes in preventing and ameliorating chemotherapy-induced oral mucositis. Based on study quality, three out of five randomized controlled trials were included in a meta-analysis. The results failed to detect any beneficial effects of chlorhexidine as compared with sterile water, or NaCl 0.9%. Patients complained about negative side-effects of chlorhexidine, including teeth discoloration and alteration of taste in two of the five studies on chlorhexidine. The severity of oral mucositis was shown to be reduced by 30% using a povidone-iodine mouthwash as compared with sterile water in a single randomized controlled trial. These results do not support the use of chlorhexidine mouthwash to prevent oral mucositis.

Keywords: oral mucositis, chemotherapy, mouthwashes, chlorhexidine, oral care.

INTRODUCTION

Oral mucositis occurs in about 40% of patients who undergo cytostatic chemotherapy for malignancies (Scully & Epstein 1996; Sonis *et al*. 2004). Virtually every patient who has undergone myeloablative therapy to prepare for a haematopoietic stem cell transplant (HSCT) develops mucositis, with 67% developing severe oral mucositis (Wardley *et al*. 2000).

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Damage to the mucous membranes (mucositis) can occur as a consequence of the direct effects of cytostatic drugs on the rapidly dividing cells in the tissues in the mouth. The initial symptoms of mucositis usually present between the fourth and seventh day after chemotherapy (Wojtaszek 2000). White discoloration of the mucous membranes mostly precedes the redness, oedema and lesions. These lesions can develop into large painful ulcers that can seriously hinder eating and drinking (Rogers 2001). Furthermore, the protective effect of saliva can be reduced – due to a decrease in the quality and quantity – increasing the chance of developing infection (Carl & Havens 2000; Epstein *et al*. 2002).

Severe mucositis results in a significant reduction in the quality of life, potential nutritional deficit and even the

postponement of chemotherapy (Bolwell *et al*. 2002). A recent study among 92 stem cell transplant recipients in eight centres in the United States, Canada and Europe demonstrated that the amount and severity of oral mucositis correlated with the number of days that patients required intravenous antibiotics, analgesics and parenteral feeding. The severity of mucositis among stem cell transplant recipients was also correlated with the number of admissions and readmissions, hospital costs and mortality (Sonis *et al*. 2001).

The high incidence and severe consequences of mucositis among patients who undergo chemotherapy underline the importance of good prevention.

Rinsing the mouth daily with chlorhexidine solution is a preventive measure frequently recommended by nurses. Solutions of sodium bicarbonate, chamomile and 0.9% saline are also often used in the Netherlands (Nieweg *et al*. 1992). The extent to which these mouthwashes actually help to prevent mucositis is unclear. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis have been produced (Rubenstein *et al*. 2004), but only two studies were used as evidence to support the use of chlorhexidine although there are more studies available in the international literature. Moreover, there was no meta-analysis. There is also a review by Clarkson *et al*. (2003) involving patients who received chemotherapy and/or radiotherapy. However, it is commonly known that mucositis induced by chemotherapy differs from that induced by radiation (Rubenstein *et al*. 2004). Therefore, we undertook to search the international literature afresh to ascertain whether these mouthwashes actually contribute to the prevention of oral mucositis among patients who undergo treatment with cytostatic chemotherapy.

METHOD

Search strategy

The Medline and Cinahl databases were searched for the relevant literature published from 1992 to the autumn of 2004. The search was restricted to these years in order to obtain maximal validity in the light of oncology care today. The search terms 'mucositis, 'stomatitis' and 'chemotherapy' were used in combination with 'prevention', 'mouthwashes', 'antiseptic', 'oral infection', 'chlorhexidine', 'chamomile', 'PVP-iodine' and 'sodium bicarbonate'.

Selection criteria

All randomized studies of the effect of mouthwashes for the prevention and amelioration of oral mucositis in adult patients undergoing chemotherapy were eligible for this systematic literature study. Two independent assessors C. P. en R. U. selected the articles. The titles and/or abstracts were used to identify those that meet the inclusion criteria. Studies were selected if they involved using mouthwashes for oral mucositis, had a controlled study design, involved adult patients with cancer who received chemotherapy and included an outcome measure of the severity of mucositis. If a difference of opinion arose, a third author was consulted before the article was included or excluded.

Study quality and analysis

The quality of a systematic review is related to the quality of the studies used with randomized controlled trials topping the hierarchy of evidence (Juni *et al*. 2001). Quality assessment allows appraisal of the studies included and also aids data synthesis. The quality of studies was assessed for randomization, blinding and the intention-to-treat analysis. In randomized controlled trials, patients are randomly assigned to either control or an experimental group. For blinding, a trial was classified as adequate if it was described as 'double-blind', a type of clinical trial in which neither the subject nor the investigator knows what treatment the patient is receiving. An intention-to-treat analysis specifies how to handle non-compliant patients in a randomized controlled trial. This analysis requires that patients be analysed in the groups into which they were randomized, regardless of whether or not they complied with the treatment allocated (Huwiler-Muntener *et al*. 2002).

In a meta-analysis or statistical pooling, the data gathered in the framework of a systematic review are statistically combined to estimate the effect of the intervention studied in the research (Thompson 1994).

The findings of the individual studies were analysed in a meta-analysis using the software Review Manager 4.2 (The Cochrane Collaboration 2002). In systematic reviews, homogeneity refers to the degree to which the results of studies included in a review are similar. A fixed effect model was allowed since homogeneity was found between the studies (Chi-squared test: $P < 0.1$).

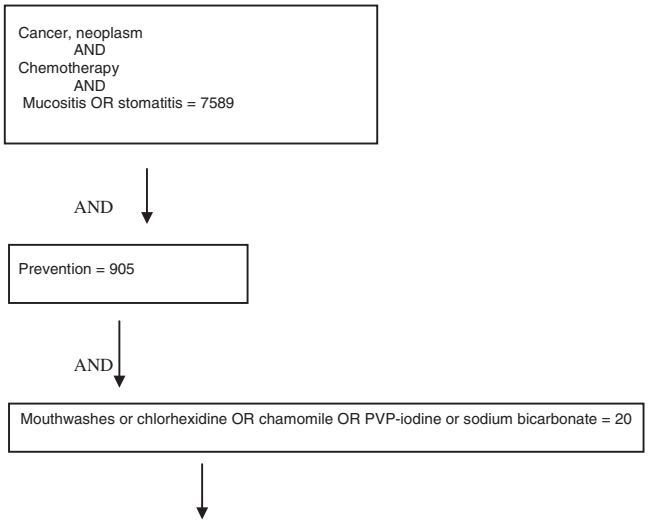
This is a statistical model that stipulates that the units under analysis (people in a trial or study in a meta-analysis) are the ones of interest, and thus constitutes the entire population of units. Only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a meta-analysis using a fixed effect model. Variation between the estimates of effect from each study (heterogeneity) does not effect the confidence interval in a fixed effect model.

RESULTS

The search term 'mucositis or stomatitis' provided 7589 hits using Medline and Cinahl for the period 1992–2004. When combined with 'prevention', there were still 905 articles. After combining with 'mouthwashes', 'antiseptic', 'oral infection', 'chlorhexidine', 'chamomile', 'PVP-iodine' or 'sodium bicarbonate', 20 articles remained (Fig. 1). Five of these studies investigated chlorhexidine in a randomized controlled clinical trial (RCT) (Epstein *et al*. 1992; Rutkauskas & Davis 1993; Dodd *et al*. 1996, 2000; Pitten *et al*. 2003). Three articles were found which investigated iodine solution as a mouthwash. However, further investigation revealed that these three articles were all reports of the same study. Hence only the most complete one is included in the review (Adamietz *et al*. 1998).

One study determined the effects of chamomile solution (Fidler *et al*. 1996). The other 11 articles were excluded: five were not RCTs but tutor reviews, two investigated dental problems and two discussed guidelines for mucositis and were therefore excluded. One study investigated micronized sucralfate versus salt and soda mouthwashes in head and neck cancer patients who received radiation therapy. This study was excluded because it dealt with radiation-induced mucositis and not chemotherapy-induced mucositis. Another study also investigated sodium bicarbonate, but did not use a randomized study design (clinical trial) and was therefore excluded.

No RCTs investigating sodium bicarbonate were found. However, three articles were found which investigated salt and soda, this solution is similar to sodium bicarbonate. In one study, where chlorhexidine was used as the intervention, the control group used a water, salt and soda solution. This study was included (Dodd *et al*. 2000).



	Inclusion	Exclusion
Chlorhexidine	5	
Chamomile	1	
PVP-iodine	1	2
Tutor reviews		5
Guidelines		2
Dental problems		2
Head and neck cancer		1
Clinical trial		1

Figure 1. Selection of articles.

Study characteristics

The seven studies (Tables 1 and 2) included data from 863 adults with cancer with a mean age of 53.6, 72% of the patients in the studies received chemotherapy, only 6% of the patients received HSCT, for 22% of the patients it is unknown which treatment was received.

The World Health Organization instrument (Miller *et al*. 1981) was used to score mucositis in three studies (Fidler *et al*. 1996; Adamietz *et al*. 1998; Pitten *et al*. 2003): one study adapted this scale (Rutkauskas & Davis 1993), two studies (Dodd *et al*. 1996, 2000) used the Oral Assessment Guide (Eilers *et al*. 1988) and one study employed a four-point scale developed by the investigator (Epstein *et al*. 1992). The frequency of assessing mucositis varied from once to twice a day, once weekly, and on three separate occasions during treatment.

Study quality

All studies randomly allocated subjects to either an intervention or a comparison group. Only one study assigned patients to one of the treatment groups by stratified block randomization (Pitten *et al*. 2003), the blocks being selected using a set of random sampling numbers. A double-blind study design was used in five studies, though the group assignment was revealed in one study at an early stage (Rutkauskas & Davis 1993). Another study had an open study design (Adamietz *et al*. 1998) and the last study did not report blinding at all (Epstein *et al*. 1992). The analysis was conducted on an intention-to-treat basis in four studies (Epstein *et al*. 1992; Fidler *et al*. 1996; Adamietz *et al*. 1998; Pitten *et al*. 2003).

Compliance

The compliance of patients with treatment has an important effect on the results of different studies, and is therefore an important element to consider (Boudes 1998). However, patient compliance was assessed in only three studies. Dodd *et al*. (2000) collected the mouth rinse bottles and measured the amounts remaining and

Table 1. Overview of randomized studies of the effect of chlorhexidine mouthwash in preventing mucositis among patients undergoing chemotherapy

Author/ year	Intervention	Dose	Control group	Number of patients*	Effect in terms of preventing mucositis	Side-effects	Successful randomization/ blinding/intention-to-treat analysis
Epstein/ 1992	Group 1. chlorhexidine 0.2% Group 2. nystatin solution 100 000 U/mL Group 3. chlorhexidine + nystatin solution	4x daily 1 min rinse with 15 mL for all groups	Salt solution	Group 1: 18 Group 2: 16 Group 3: 34 Control group: 18 Power ≤80	Max mucositis† 1: mean 3.53 2: mean 3.45 3: mean 3.95 c: mean 2.46	Not stated	Yes/Unknown/Yes
Rutkauskas/ 1993	Chlorhexidine 0.12%	2x daily 30 s rinse with 15 mL	Mouthwash without chlorhexidine	Intervention group: 10 Control group: 11	None‡ (no numbers stated in the publication)	Brown discoloration of the teeth and altered taste in chlorhexidine group. Number and severity not stated.	Yes/Incomplete/No Unblinded early. Excluded patients $n = 8$ did not tolerate mouth inspection.
Dodd/ 1996	Chlorhexidine 0.12%	2x daily 20 s rinse with 20 mL	Sterile water	Intervention group: 112 Control group: 110 Power >80	Mucositis§ present/severity: Intervention group. 28%/mean 14.10 95% CI. ±26%/ mean 13.79	Not stated	Yes/Complete/No 51 patients dropped from the study. Discontinued, death, month wash taste unpleasant
Dodd/ 2000	Group 1. 1 teaspoon salt + 1 teaspoon soda in 454 mL water Group 2. chlorhexidine 0.12% Group 3. Magic = 5 mL lidocaine solution (0.5%) + 0.25 mL diphenhydramine hydrochloride + 14.75 mL aluminium hydroxide	4x daily 20 s rinse with 20 mL	None	Group 1: 48 Group 2: 51 Group 3: 42 Power >80	Severity mucositis§ 1: mean 13.21 2: mean 13.71 3: mean 13.81	Unpleasant sensation in the chlorhexidine group Number not stated	Yes/Complete/No Excluded patients $n = 58$. Too ill, too painful, nauseous, groups remained comparable
Pitten/2003	Chlorhexidine 0.3% (Skinsept mucosa®)	3x daily 30 s rinse with 20 mL	Amine-stannous fluoride (Meridol®)	Intervention group: 24 Control group: 23 Power ≤80	Severe mucositis¶ Odds ratio 6.3 (1.02–49.67)	Uncomfortable or painful	Yes (block randomized)/ Complete/Yes

*Power calculation assuming $\alpha = 0.05$, $\Delta = 20\%$ in frequencies or 20% of scale range.
†Four-point scale developed for this study.
‡Adapted World Health Organization four-point scale.
§Oral Assessment Guide.
¶World Health Organization scale.

Table 2. Overview of the effect of mouthwashes other than chlorhexidine in preventing mucositis among patients undergoing chemotherapy

Author/ year	Intervention	Dose	Control group	Number of patients*	Effect in terms of preventing mucositis	Side-effects	Successful randomization/ blinding/ intention-to-treat analysis
Fidler/ 1996	20 drops chamomile solution in 100 mL water	3x daily 1 min rinse 3 to 5x	Mouthwash without chamomile	Intervention group: 82 Control group: 82 Power ≤80	Mucositis score† Physician: intervention. 40% control 45% Patient intervention. 49% control 61%	Chamomile was well tolerated with no increase in nausea and vomiting	Yes/Complete/Yes
Adamietz/ 1998	PVP-iodine betaisodona®	3 min rinse 4x daily	Sterile water	Intervention group: 20 Control group: 20 Power ≤80	Mucositis score‡ intervention. 70% control 100%	None: as long as the iodine was not swallowed as then there is a risk of hyperthyroidism	Yes/No, open/Yes

*Power calculation assuming $\alpha = 0.05$, $\Delta = 20\%$ in frequencies or 20% of scale range.
†World Health Organization scale.
‡Oral Assessment Guide.

compared this with what should have been used. Compliance in this study was very high (92%), although it is not known if patients disposed of their mouth rinses in another manner, but the investigators had no reason to believe that this occurred. However, Epstein *et al*. (1992) found less positive results regarding compliance with rinsing. In their study, assessment of compliance was based on medication records and on an interview at weekly assessment visits. Patients assigned to rinsing with Nystatin alone or in combination with chlorhexidine showed poor compliance, with only 47% of patients in the nystatin-chlorhexidine rinse group using the rinse a 100% of the time, 78% of patients using chlorhexidine at all times, but 89% of them using the saline solution group at all times.

Pitten *et al*. (2003) used brown glass bottles. On visiting the patients to assess mucositis, the clinician checked if the volume remaining in the bottle correlated with the number of rinses. The findings indicated that the patients had rinsed properly.

Chlorhexidine

Chlorhexidine is approved for use as an antibacterial mouthwash at a concentration of 0.12% and 0.2% to prevent the build-up of dental plaque and to prevent gingivitis (Yates *et al*. 2002). Its broad spectrum of antibacterial activity, minimal systemic absorption and ability to bind to oral surfaces led to use as prophylaxis in an attempt to prevent the development of oral mucositis (Matthijs & Adriaens 2002).

Chlorhexidine has been tested in five randomized studies for its effects in preventing oral mucositis in patients undergoing chemotherapy Table 1.

Epstein *et al*. (1992) investigated three different mouthwashes, chlorhexidine, nystatin and a combination of nystatin-chlorhexidine and compared these with rinsing using a saline solution. All patients ($n = 86$) who received medical therapy that resulted in severe neutropenia were included into the study. Fifty-six patients (65%) received aggressive chemotherapy for remission induction or consolidation. Thirty patients (35%) received HSCT. The patients were asked to rinse with the mouthwash after eating. Oral hygiene was assessed using the gingival index and plaque levels, and mucositis was assessed using a four-point scale specially developed for the study. Bacterial and fungal oral cultures were done on a weekly basis. There was no difference in mucositis between the four groups although bacterial and fungal infections were found less often among the patients using chlorhexidine.

Rutkauskas and Davis (1993) investigated the effect of chlorhexidine versus a placebo in patients undergoing HSCT or remission-indication chemotherapy. The study showed chlorhexidine to be ineffective in preventing mucositis. Unfortunately, the data were also presented in a form that made it impossible to include them in the meta-analysis.

Dodd *et al*. (1996) investigated the effect of an instruction programme for the systematic oral care of 222 patients undergoing chemotherapy provided by nurses in combination with two mouthwashes (chlorhexidine and sterile water). The preventative effects of rinsing with chlorhexidine were no greater than those of rinsing with sterile water leading the investigators to recommended rinsing with water only.

Dodd *et al*. (2000) also compared the preventative effects of three mouthwashes (chlorhexidine, salt and soda in water) and 'magic mouthwash' (containing Lidocaine, Benadryl and Maalox) in patients who received stomatotoxic chemotherapy at home and were monitored on an outpatient basis. Nurses used the Oral Assessment Guide for initial assessment, instructed patients on how to assess their own mouths, then phoned the patients every other day to note their oral status. No differences in the severity of mucositis were found between the three groups nor were there any significant differences in the time taken for signs and symptoms of mucositis to subside. The first signs of mucositis were seen within 6.6 days in the chlorhexidine group, within 7.0 days in the water/salt/soda group and within 7.2 days in the 'magic mouthwash' group.

Pitten *et al*. (2003) investigated chlorhexidine versus amine-stannous fluoride solution to investigate whether leucopenic patients who cannot clean their teeth mechanically might have clinical benefit from an antiseptic mouth rinse containing chlorhexidine. The statistical analysis showed that there was a significant decrease in the numbers of microorganisms in the oral cavity during leucopenia among those in the chlorhexidine group compared with that in the control group. However, this did not translate into any measurable clinical benefit. Patients rinsing with chlorhexidine also indicated that the rinsing was unpleasant and even painful.

Power

None of the studies reported a power calculation, so we calculated this from the numbers of patients reported, assuming an alpha of 0.05 (two-sided) and a clinically relevant effect size of 20% of the scale range for severity of mucositis in several studies, or a 20% difference in frequencies in studies with presence or absence of mucositis as the main outcome. Only the studies by Dodd *et al*. (1996, 2000) had sufficient power (≥80%). The study by Fidlet *et al*. had an estimated power of 70% (Fidler *et al*. 1996), whereas the power of the other studies was less.

Meta-analysis

Within the meta-analysis, the results from individual studies were weighted in inverse proportion to their variance, resulting in a weight proprtional to the size of the studies.

Four out of five studies that investigated chlorhexidine mouthwash for preventing mucositis were eligible for inclusion in the meta-analysis. Rutkauskas and Davis (1993) and Pitten *et al*. (2003) did not state all of the necessary figures for this. The study by Epstein *et al*. (1992) had a total of four groups and in the analysis was approached as two studies, namely chlorhexidine versus saline solution and chlorhexidine + nystatin versus nystatin.

The study by Dodd *et al*. (2000) was also entered as two studies (chlorhexidine vs. water/salt and soda and chlorhexidine vs. 'magic mouthwash').

All the information is contained within the forest plot graphical representation of the results in Figure 2.

Taken together the results, the five studies showed no significant effect of chlorhexidine mouthwash (Weighted mean differences 0.22; 95% confidence interval = –0.20, 0.63). The test for heterogeneity and the test for overall effect are given at the bottom of the forest plot. It is important to remember that heterogeneity may be present when all or most studies indicate the same treatment effect, but the size of the effect differs or the trials are contradictory about the effect (Sutton *et al*. 1998). The results are considered homogenous when the effect sizes differ due to sampling errors.

Other mouthwashes

Table 2 provides an overview of randomized studies into the effect of mouthwashes other than chlorhexidine in preventing mucositis in patients undergoing chemotherapy.

Fidler *et al*. (1996) evaluated the effect of a chamomile solution in a group with a total of 164 patients treated with 5-FU chemotherapy. After randomization, 82 patients received a mouthwash with a chamomile solution and 82 patients received a mouthwash without. All patients received oral cryotherapy for 30 min with each

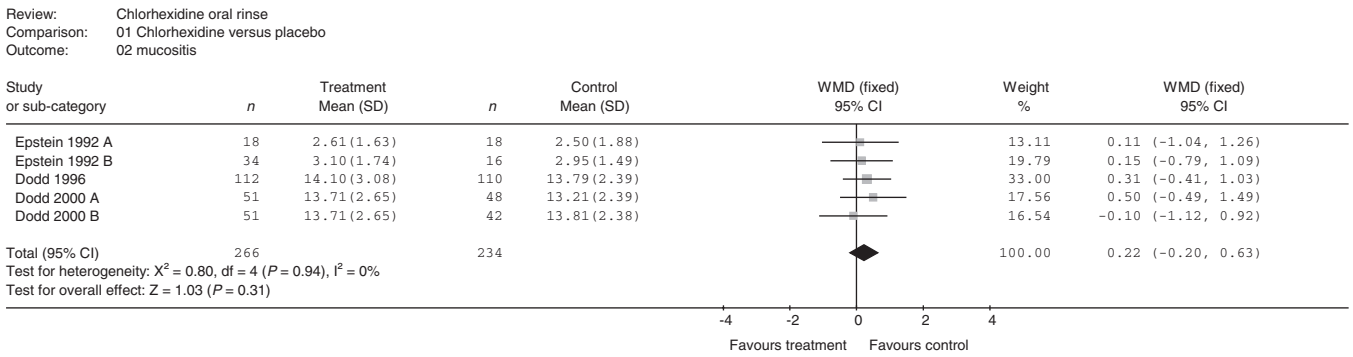


Figure 2. Forest plot of mean (SD) mucositis scores. CI, confidence interval; SD, standard deviation; WMD, weighted mean difference.

dose of 5-FU. Mucositis was scored by the physician (scale of 0–4). The patient also recorded his or her score on a daily basis. No differences were found between the chamomile group and the control group in either the incidence or severity of mucositis.

Adamietz *et al*. (1998) investigated the preventative effects of iodine solution as a mouthwash compared with rinsing with water in 40 patients given radiochemotherapy ($n = 20$ for both groups). The World Health Organization criteria for mucositis (scale of 0–4) were used to estimate the severity and duration of the mucositis. The iodine group had a significantly less severe mucositis compared with the control group and the duration of the mucositis was shorter (2.8 weeks for the iodine group vs. 9.3 weeks for the control group). However, the study was too small to be confident that the difference observed was not simply a chance finding.

CONCLUSION

A systematic review was used to assemble and synthesize the evidence for the effect of commonly used mouthwashes on the prevention of chemotherapy-induced oral mucositis. Comprehensive search methods were used to minimize any bias.

With the exception of iodine solution, none of the studies investigated were able to demonstrate an effect in preventing mucositis in patients undergoing chemotherapy.

Chlorhexidine

Chlorhexidine is widely used and has been investigated albeit in various small studies. Individually, the studies found chlorhexidine to be ineffective and increasing power through meta-analysis did not alter this. Studies done before 1992 found a positive effect of rinsing with chlorhexidine (McGaw & Belch 1985; Ferretti *et al*. 1988, 1990) whereas those conducted in the period 1992–2004 found either no effect or a negative effect. One possible explanation could be that bacterial infections were better controlled and managed after 1992 than before because of better antibiotics.

The discoloration of teeth, the bitter taste and the unpleasant sensation experienced together with ineffectiveness are sufficient reasons for recommending sterile water, 0.9% saline solution or sodium bicarbonate (water, salt and soda) rather than chlorhexidine. Furthermore, these alternatives are less expensive and readily available in everyday nursing practice.

Other mouthwashes

Most of the other formulations had no effect on the prevention of mucositis. The antifungal drug nystatin, even in combination with chlorhexidine, was no exception (Epstein *et al*. 1992).

Even chamomile, which has an anti-inflammatory effect, proved ineffective. (Carl & Emrich 1991).

One study did demonstrate that iodine solution was effective as a mouthwash, but this finding must be treated with caution, due to the small sample sizes involved. Moreover, side-effects were not reported, though, when accidentally swallowed, iodine can cause hyperthyroidism.

The sample sizes varied from 21 to 222 and none of the studies indicated the power calculation based on a proposed treatment effect even though adequate statistical power is crucial to minimize type-II or beta errors (Cohen 1992). This shortcoming was compensated to some extent by the meta-analysis supporting the negative conclusions for chlorhexidine, which does not apply to other mouthwashes.

Patient compliance with the intervention has an important effect on the results and should always be considered (Boudes 1998), yet only three studies did so (Epstein *et al*. 1992; Dodd *et al*. 2000, Pitten *et al*. 2003).

Based on our findings and those of others (Clarkson *et al*. 2003; Rubenstein *et al*. 2004), the use of chlorhexidine as well as other mouthwash for preventing oral mucositis in patients undergoing chemotherapy cannot be recommended. The use of an iodine solution could be promising, but should be investigated further.

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