CRD summary
This review found that iodine was an effective and safe antiseptic agent that enhanced wound healing, particularly in chronic and burn wounds. Parts of the review were well-conducted, but concerns about the method of synthesis and the suboptimal quality of the included trials mean that the reliability of the authors’ conclusion is unclear.

Authors' objectives
To evaluate the effects of iodine in the treatment of different types of contaminated wounds.

Searching
MEDLINE, CINAHL and EMBASE were searched with no language restrictions from inception to August 2008. The Cochrane Central Register of Controlled Trials (CENTRAL) was also searched up to Issue 3, 2008. Reference lists of relevant articles were checked to identify additional references. There were no restrictions on the basis of publication status or date.

Study selection
Randomised controlled trials that evaluated iodine-containing wound care products compared with any control treatment in patients with any type of contaminated wound were eligible for inclusion.

The primary endpoints were bacterial load or wound infection, and wound healing. Wound healing was defined as time to complete healing, change in wound surface, survival rate of split-thickness grafts and wound readiness for surgical closure. Secondary endpoints were adverse events, costs and length of hospital stay.

The included trials were conducted in Europe, the USA, the United Arab Emirates, India, Australia, and South Africa; seven trials were performed in the UK. Included patients were aged up to 102 years (where reported). The types of wounds treated were chronic and pressure ulcers, acute and burn wounds, and skin grafts. Various iodine treatments used in the trials, with components that included: cadexomer iodine, povidone iodine with and without zinc oxide-impregnated gauze, neosporin or compression; tri-iodine solutions of potassium iodide and iodine crystals; polyvinylpyrrolidine-I hydrogel complexes, wound wicks soaked in 1% povidone iodine, and polyvinylpyrrolidone and a number of branded treatments. A range of control treatments were used including honey, hydrocolloid, hydrofibre and saline dressings; subcuticular suture; silver sulfadiazine; paraffin gauzes; debriding agents; a number of branded treatments; and best treatment in the physician's opinion.

Two reviewers performed the study selection; any disagreements were resolved by discussion.

Assessment of study quality
Three reviewers independently assessed methodological quality using the Dutch Cochrane Collaboration Checklist with some relevant criteria added. Any disagreement between the reviewers was resolved by discussion.

Data extraction
Data were extracted by one reviewer to calculate summary estimates of treatment effect. A second reviewer checked the extracted data. Mean differences (MDs), with 95% confidence intervals (CIs), were calculated for continuous outcomes; risk differences (RDs), with 95% confidence intervals, were calculated for dichotomous outcomes. In the event of missing data, attempts were made to contact the trial authors.

Methods of synthesis
A meta-analysis, using a random-effects model, was planned where there was clinical homogeneity and statistical heterogeneity ($I^2<60\%$), but this was not conducted due to clinical heterogeneity. Instead, the data were presented in vote-counting tables. Statistical differences in vote-counting totals were calculated with the McNemar sign test. These tables were presented alongside a narrative summary, where the results were grouped by wound type and outcome.
Results of the review
Twenty-seven RCTs (n=4,495 patients) were included in the review. The sample sizes in the trials ranged between 27 and 1,089 patients. The overall quality of the included trials was limited. From the supplementary table: 18 trials reported some form of randomisation; allocation concealment was reported in 12 trials; five trials reported using an independent outcome assessor; intention-to-treat analyses were performed in 10 trials; 20 trials had more than 80% follow-up of patients.

Chronic ulcers (12 trials): Beneficial effects were found of iodine in complete wound healing (seven trials) and reductions in wound surface were observed (six trials). Six trials showed a benefit of control treatments in wound pain. Of 20 outcome comparisons (seven trials) that evaluated adverse effects of iodine compared with other wound dressings or topical agents, five comparisons showed significant benefits of iodine and four comparisons showed significant beneficial changes with other dressings. All adverse events were reversible with no serious sequelae.

Pressure ulcers (three trials): The iodine-containing substances povidone or cadexomer iodine were associated with significant benefits in three wound healing outcomes, although for two healing outcomes there were benefits observed with other debriding or antiseptic agents/dressings. In one trial, there were no differences in pain scores, but significantly more mild adverse events were found in the cadexomer iodine group.

Acute wounds (seven trials): There were few differences found between iodine-containing solutions and control treatments in wound healing or bacterial load and infection rates. Iodine caused less hypergranulation than the control treatment of Intrasite gel, but more wound trauma than a silver-containing hydrofibre. Lengthened hospital stays were associated with iodine plus alcohol treatment compared with treatment with honey.

Burn wounds (three trials): Three trials showed significantly faster wound healing times with iodine-containing solutions compared with control treatments. Adverse event rates did not differ between iodine treatments and chlorhexidine-impregnated gauzes or silver sulfadiazine.

Skin grafts (two datasets): There were no differences in bacterial load and infection between povidone iodine and paraffin gauze, although povidone iodine was significantly associated with less time to wound healing and less graft loss. There were no harmful effects on thyroid function observed with iodine treatment.

Cost information
Two trials reported cost data for chronic wounds.

One trial found the mean total weekly costs were 111 US dollars ($) for iodine compared with $175 for the control group. The weekly costs for the healed patients were $379 for iodine compared with the control group cost of $1,579 (control group patients received gentamicin solution, streptodornase or saline gauzes).

One trial calculated material costs per day, which were $3.00 for cadexomer iodine paste, $0.65 for hydrocolloid dressings, and $0.09 for paraffin gauze dressings.

Authors' conclusions
Based on the available evidence, iodine was an effective antiseptic agent that was not associated with adverse side effects or delays in the healing process, particularly for chronic and burn wounds. The antiseptic effects of iodine were not inferior to other antiseptic agents and did not impair wound healing.

CRD commentary
The review addressed a question that was broad in scope. Criteria for the inclusion of studies were clearly outlined. Appropriate databases were searched. There were some attempts to identify unpublished studies. Steps to minimise errors and bias at each stage of the review process were reported in the review.

An appropriate quality assessment tool was applied; the overall quality of the included trials was limited. Given the clinical heterogeneity between treatments, wound types and outcome parameters in the included trials, the authors were justified in refraining from statistical pooling of results. The authors used vote-counting tables as a means of summary;
they acknowledged the limitations of this method.

The review was generally well conducted, but concerns about the method of synthesis and the suboptimal quality of included trials mean that the reliability of the authors’ conclusion is unclear.

Implications of the review for practice and research

Practice: The authors stated that, given the increasing microbial resistance against antibiotics, clinicians should rely more heavily on the use of antiseptic remedies instead of local antibiotics if an indication for the use of antimicrobials is present.

Research: The authors stated that high-quality RCTs are required to determine the effectiveness of iodine in treating and preventing wound infection, to find the optimum method of iodine administration, to compare iodine with other antiseptic agents, and to clearly define the use of iodine in present-day wound care. They recommended that future studies should examine the cost-effectiveness of antiseptics.

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