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Review

Benefit and harm of iodine in wound care: a systematic review

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SUMMARY

Nowadays many products are available to combat infections and thus to promote wound healing. Iodine is one of these products, but reports are conflicting as to the effectiveness and adverse effects of iodine in the treatment of wounds. A systematic review was performed of 27 randomised clinical trials, reporting on chronic, acute, burn wounds, pressure sores, and skin grafts. Main outcome parameters were wound healing, bacterial count, and adverse effects. Iodine did not lead to a reduction or prolongation of wound-healing time compared with other (antiseptic) wound dressings or agents. In individual trials, iodine was significantly superior to other antiseptic agents (such as silver sulfadiazine cream) and non-antiseptic dressings, but seemed inferior to a local antibiotic (Rifamycin SV MMX®) and, when combined with alcohol, to crude honey in reducing bacterial count and/or wound size. Adverse effects, including thyroid function derailment, did not occur more frequently with iodine. Based on the available evidence from clinical trials, iodine is an effective antiseptic agent that shows neither the purported harmful effects nor a delay of the wound-healing process, particularly in chronic and burn wounds. The antiseptic effect of iodine is not inferior to that of other (antiseptic) agents and does not impair wound healing. Hence, iodine deserves to retain its place among the modern antiseptic agents.

Introduction

Wound healing can be negatively influenced by many factors. One major contributor of impaired healing is wound infection, due to a plethora of pathogens. It is therefore not surprising, considering the increasing prevalence of multi-resistant micro-organisms in hospitals, that many (modern) antiseptic products such as silver, honey and (local) antibiotics are available to prevent and combat wound infection.

Iodine is probably the best known antiseptic and has been used for more than a century.[1] However, the use of iodine to treat or prevent wound infection is under discussion. Iodine (as well as antiseptics in general) in wound treatment is believed to cause allergic reactions, to be less effective due to poor penetration, or to negatively influence tissue regeneration due to a toxic effect on the host cells.[2–4] These reports, however, were published more than 25 years ago.

On the other hand, other reports suggest that these fears may be unjustified as they are based on sometimes inappropriately performed studies with animals, or in a laboratory setting with standardised wound conditions, and are therefore not applicable to humans.[5,6]

In this systematic review of randomised clinical trials (RCTs) we investigated the possible beneficial and harmful clinical effects of iodine in the treatment of all kinds of (contaminated) wounds.

Methods

Literature search

The search for potentially relevant RCTs was performed in Cinahl, Embase, and Medline, from inception of the databases to August 2008, and the Cochrane Controlled Trials Register up to Issue 3, 2008. The searches were performed without restrictions on language, publication date, or publication status. In addition, references in relevant articles were searched for other potentially relevant publications.

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Inclusion criteria

Eligible RCTs needed to report on a local wound care product containing iodine in patients with any kind of (more or less contaminated) wound. Any concentration or manufacturer of iodine as well as any type of control treatment was allowed.

Primary endpoints were bacterial load or wound infection and wound healing (expressed as time to complete healing, change in wound surface, survival rate of split-thickness skin grafts, and wound ready for surgical closure).

Secondary endpoints were adverse events (such as pain and erythema), costs, and length of hospital stay.

Study selection

Titles and abstracts of studies identified by the search strategy were assessed by two reviewers (H.V. and D.U.) independently in terms of relevance and design. Any disagreement was solved by discussion. The full versions of the articles were obtained if they fulfilled the selection criteria.

Study quality

Methodological quality of each trial was assessed systematically and independently (S.W., H.V. and D.U.) with the aid of the Dutch Cochrane Collaboration checklist (online), extended with some other relevant criteria. Again, any disagreement was solved by discussion.

Data extraction

Trial data were extracted and summarised by one investigator (S.W.) and checked by a second reviewer independently (D.U.). Data included trial and patient characteristics, and details on interventions and outcomes. Attempts were made to contact trial authors in order to settle any uncertainties.

Data analysis

Quantitative data were entered and analysed in RevMan 4.2.8 (Cochrane Collaboration). For each outcome, summary estimates of treatment effect [with 95% confidence interval (CI)] were calculated for every comparison. For continuous outcomes, mean difference (MD) was presented. For dichotomous outcomes, the absolute risk reduction, i.e. risk difference (RD), was presented, which is an absolute effect measure that expresses the difference between the experimental and the control event rates and allows calculation of the number needed to treat (NNT).

Meta-analysis was planned only in case of clinical homogeneity and statistical heterogeneity, as expressed by means of the I^2 statistic, of $<60\%$, using a random effects model. If meta-analyses were impossible, individual study data were presented, which were also summarised in vote-counting tables. Such tables show the number of studies in favour or against the index intervention (iodine), irrespective of the size of the treatment effect found, in order to estimate a general tendency as to the effectiveness of the index intervention. Statistical analysis of the differences in vote count totals in favour or against iodine was performed with the McNemar sign test.

Results

The search yielded 266 potentially relevant studies. Of these, 29 publications met our inclusion criteria. Trial flow and reasons for exclusion are shown in Figure 1.

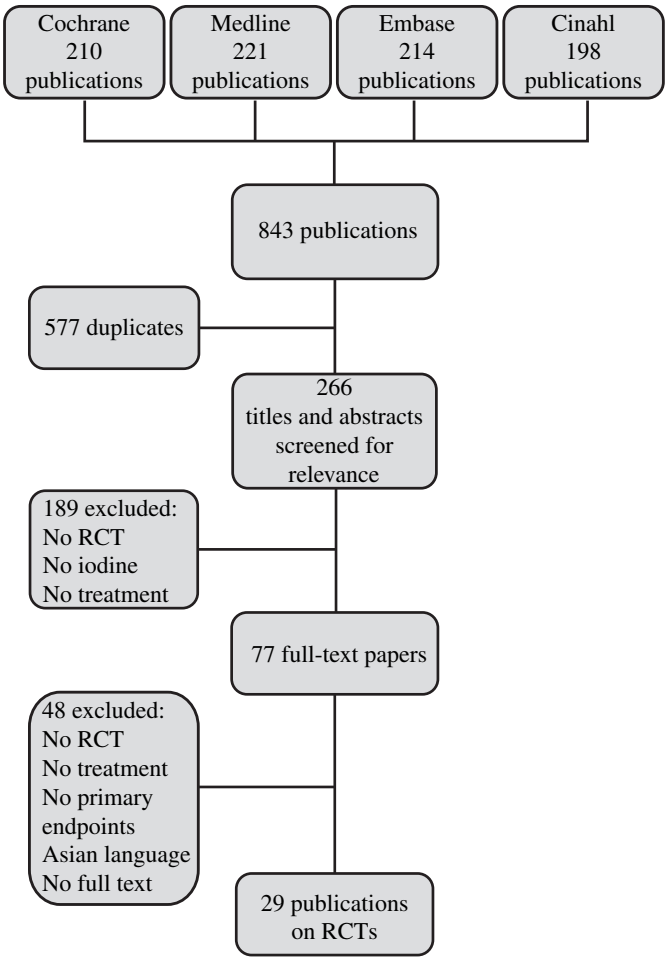

Figure 1. Flow chart of trial inclusion. RCT, randomised controlled trial.

Of the 29 studies included, Reimer *et al.* and Vogt *et al.* used the same patient set as did Hauser *et al.* and Vogt *et al.*[7–10] Thus, this review comprised 29 publications on 27 RCTs. Relevant data were extracted from all publications. Trial sizes ranged from 27 to 1089 patients, totalling 4495. More than half (52%) of the trials were published more than 10 years ago. For a detailed description of the studies included see Table I.

Table S1 supplies a complete listing of the methodological characteristics. Overall trial quality was limited. The most common flaws are mentioned below. Four out of the 27 trials (15%) used a form of quasi-randomisation, if described at all. Allocation concealment was applied and described in 11 trials (41%). The intention-to-treat principle was mentioned in 10 trials (37%). The nature of the treatment made blinding of patients and healthcare professionals impossible. Only five trials (19%) declared the use of an independent outcome assessor. Nine trials (33%) declared sponsorship by a manufacturer of medical devices.

In the 29 publications on RCTs found, a large variety of wound care products, wound types, and outcome parameters were investigated (Table I). Because of this clinical heterogeneity no meta-analyses could be performed. The results are categorised by the various wound types studied.

Chronic wounds

In 12 trials the effectiveness and possible harm of iodine was studied in patients with chronic ulcers.[11–22] Many different

Table I
Characteristics of the 29 included publications on 27 studies

Publication	Trial characteristics[a]	Patients[b]	Intervention[c]	Outcomes	Remarks
Al-Waili and Saloom[26]	1. Unknown 2. Up to 1 month 3. 24/26 4. Hospital 5. 1 6. United Arab Emirates 7. None reported	1. 25 years 2. Postoperative wound infections following caesarean sections and hysterectomies	1. 70% ethanol and povidone iodine 2. Honey	Culture, healing, hospital stay, antibiotics use, scar size	
Altman *et al.*[11]	1. Every alternating case 2. Up to 14 months 3. 72/88 4. Outpatient 5. 1 6. USA 7. None reported	1. Mean not reported age range 32–87 years 2. Patients with chronic leg ulcers and gangrenous lesions in the vascular clinic	1. Tri-iodine solution (0.5 g potassium iodide in 100 mL of water with 0.5–1.0 g iodine crystals) 2. Best treatment in physician's opinion	Healing time	Preliminary report, subgroup study
Apelqvist *et al.*[14]	1. Computer-generated list 2. 12 weeks 3. 22/19 4. Outpatient 5. 1 6. Sweden 7. Perstorp Pharma (Iodosorb®), Swedish Diabetic Association	1. Not reported 2. Diabetic patients with exudative foot ulcers below the ankle	1. Cadexomer iodine (Iodosorb®) 2. Gentamicin solution; Garamycin®, streptodornase; Varidase®, dry saline gauze; Mesalt®	Complete healing or >50% ulcer area reduction, costs	
Daróczy[15]	1. Unknown 2. 12 weeks up to 5 months 3. 21/21/21 4. Outpatient 5. 1 6. Hungary 7. None reported	1. 58 years 2. Patients with ulcerated stasis dermatitis due to deep venous refluxes	1. Povidone iodine (Povidone) with compression 2. Betadine® without compression, and amoxicillin	Healing rate, elapse of superficial bacterial infection	Three treatment groups
Denning[31]	1. Day of surgery 2. Till wound closure 3. 36/58 4. Outpatient 5. 1 6. England 7. None reported	1. 38 years for the iodine group/32 years for the control group 2. Patients requiring nail surgery	1. Povidone iodine (Inadine®) 2. Release®	Healing time, infection rate	
Dovison and Keenan[30]	1. Not reported 2. Until wound healing; up to 2 months 3. 13/13/16 4. Outpatient 5. 2 6. Australia 7. Patim Pty Ltd (research grant), Briggate Medical Supplies	1. Not reported 2. phenolised partial nail avulsion wounds of hallux	1. Betadine® (10% povidone iodine) 2. Paraffin gauze, and intrasite gel and paraffin	Healing time, clinical infection rate	Three treatment groups
Groenewald[12]	1. Not reported 2. 21 days 3. 50/50 4. Outpatient 5. 1 6. South Africa 7. None reported	1. Not reported 2. Patients with chronic venous leg ulcers	1. Povidone iodine and zinc oxide-impregnated gauze 2. Debrisan®	Healing time, wound cleansing, wound size reduction, graft take, oedema, pain, bacterial contamination	
Han and Maitra[33]	1. Random permuted block allocation 2. Till complete healing, max. 53 days 3. 111/102 4. Hospital/outpatient 5. 1 6. England 7. None reported	1. Not reported, range 0–75 years 2. Patients with <10% TBS partial thickness burns	1. Inadine® 2. Bactigras®	Bleeding, pain, visits, treatment time, off work, contamination	
Hansson[16]	1. Not reported 2. 12 weeks 3. 56/48/49 4. Outpatient 5. 4 6. Sweden, Denmark, Netherlands, and UK 7. Perstorp Pharma	1. 74 years in the iodine group, 74 and 72 years in the two others 2. Patients with exudating or sloughy venous leg ulcers	1. Cadexomer iodine (Iodosorb®/Iodoflex®) 2. Hydrocolloid dressing (Duoderm E®, Granuflex®), and gauze dressing (Jelonet®)	Ulcer size, stop exudation, costs	Three treatment groups
Hauser *et al.*[9]	See Vogt *et al.* (2006)[10]	See Vogt *et al.* (2006)[10]	See Vogt *et al.* (2006)[10]	See Vogt *et al.* (2006)[10]	Same dataset as Vogt *et al.* (2006)[10]

(*continued on next page*)

Table I (*continued*)

Publication	Trial characteristics[a]	Patients[b]	Intervention[c]	Outcomes	Remarks
Holloway *et al.*[20]	1. Not reported 2. 24 weeks; cross-over at 12 weeks 3. 38/37 4. Outpatient 5. 4 6. USA 7. TIL Medical Ltd	1. 63 in the iodine group/61 in the control 2. Patients with a venous stasis ulcer present for >3 months	1. Cadexomer dressing 2. Saline wet-to-dry dressing	Wound healing, pain, wound condition	
Homann *et al.*[34]	1. Programme Rancode 3.6 2. 21 days 3. 43/43 4. In- and outpatient 5. 5 6. Germany 7. Mundipharma GmbH	1. 37.2 2. Patient with two partial thickness burn wounds	1. PVP-I hydrogel Repithel® 2. Flammazine®	Wound healing, safety	Two wounds in each patient randomised to receive either treatment
Iselin *et al.*[27]	1. Chronological order 2. Up to 4 weeks 3. 134/134 4. Hospital? 5. 1 6. France 7. None reported	1. 33 in the iodine group/30 in the control 2. Patients presenting in the emergency hand surgery	1. Povidone iodine 2. Rifamycin SV MMX®	Healing rate, infection, adverse effects	
Jurczak *et al.*[28]	1. Sealed envelopes 2. 2 weeks 3. 32/35 4. Hospital 5. 7 6. Germany, France, Great Britain 7. ConvaTec	1. 43 in the iodine group/34 in the control 2. Patients with an open surgical or traumatic wound	1. Povidone-iodine 2. Hydrofibre Ag dressing	Pain, change in wound size, comfort, bleeding, dressing removal	
Kaya *et al.*[23]	1. Not reported 2. Till complete healing 3. 15/12 4. Hospital 5. 1 6. Turkey 7. None reported	1. 30 in the iodine group/35 in the control 2. Patients with spinal cord injury having pressure ulcers	1. Povidone-iodine gauze 2. Hydrogel-type dressing (Elasto-gel®)	Healing rate	
Kucan *et al.*[25]	1. Computer-generated table 2. 21 days 3. 11/14/15 4. Hospital 5. 1 6. USA 7. None reported	1. Not reported, range 16–102 2. Patients with chronic pressure ulcers	1. Povidone iodine 2. 0.9% NaCl solution, and silver sulfadiazine	Bacterial count, clinical response	Three treatment groups
Laudanska and Gustavson[13]	1. Not reported 2. 6 weeks 3. 30/30 4. Hospital 5. 1 6. Sweden 7. None reported	1. 64.8 in the iodine group/63.5 in the control 2. Patients with chronic venous ulcers	1. Cadexomer iodine (Iodosorb®) 2. Zinc paste dressing, saline dressing, and Gentian Violet	Reduction in ulcer size and healing within 6 weeks	
McCreal *et al.*[29]	1. Sealed envelope 2. 4 weeks 3. 86/88 4. First hospital, later outpatient 5. 1 6. Ireland 7. Not reported	1. 20.5 in the iodine group/23 in the control 2. Patients who underwent appendicectomy	1. Wound wick soaked in 1% povidone iodine 2. Subcuticular suture	Infection rate and time to wound healing, patient discomfort and cosmetic result	
Michiels *et al.*[32]	1. Randomisation list 2. 12 days 3. 20/20 4. Hospital 5. 2 6. Belgium 7. None reported	1. 45.2 in the iodine group/45.5 in the control 2. Patients with infected postoperative wounds	1. Polyvinylpyrrolidone 2. Dextranomer paste (Debrisan®)	Cleansing, inflammation reduction, wound healing	Children in study
Moberg *et al.*[24]	1. Unknown 2. 8 weeks 3. 19/19 4. Hospital 5. 2 6. Sweden 7. None reported	1. 72.6 in the iodine group/80.1 in the control 2. Patients with pressure ulcers	1. Cadexomer iodine 2. Saline dressings, debriding agents, non-adhesive dressings	Wound area reduction, pain, and pus and debris	Partial cross-over at 3 weeks

Table I (*continued*)

Publication	Trial characteristics[a]	Patients[b]	Intervention[c]	Outcomes	Remarks
Moss *et al.*[21]	1. Unknown 2. 26 weeks 3. 21/21 4. Outpatient 5. 1 6. UK 7. TIL Medical Ltd	1. 70 in the iodine group/68 in the control 2. Patients with chronic resistant varicose ulcers	1. Cadexomer iodine 2. Dextranomer	Ulcer reduction, bacterial load	Partial cross-over at 6 weeks
Ormiston *et al.*[17]	1. Sealed envelope 2. 24 weeks 3. 30/30 4. Outpatient 5. 1 6. UK 7. TIL Medical Ltd and Perstorp	1. 67.3 in the iodine group/70.3 in the control 2. Patients with chronic resistant varicose ulcers present for >3 months	1. Cadexomer iodine 2. Gentian Violet and Polyfax® ointment	Healing rate cm^2/week, granulation, oedema, pain, exudates, pus and debris, and erythema	Partial cross-over at 12 weeks
Reimer *et al.*[7]	See Vogt *et al.*[8]	See Vogt *et al.*[8]	See Vogt *et al.*[8]	See Vogt *et al.*[8]	Same data set as Vogt *et al.*[8]
Sinha *et al.*[35]	1. Alternatively 2. 46 days 3. 1053/1089 4. Hospital 5. 1 6. India 7. None reported	1. Not reported 2. Patients with superficial burns	1. Povidone iodine + neosporin 2. Silver sulfadiazine	Bacterial counts, rate of epithelialisation and mortality	
Skog *et al.*[22]	1. Not reported 2. 6 weeks 3. 38/36 4. Outpatient 5. Multicentre 6. Sweden, and Norway 7. TIL Medical Ltd	1. 68.1 in the iodine group/72.1 in the control 2. Patients with chronic venous ulcers	1. Cadexomer iodine powder 2. Mostly paraffin-impregnated gauze and saline	Change in ulcer size, pain, pus and debris exudates, granulation, erythema, and oedema	
Smith *et al.*[18]	1. Block randomisation 2. 4 months 3. 101/99 4. Outpatient 5. 1 6. UK 7. Clinimed Ltd	1. 73 in the iodine group/75 in the control 2. Patients with a venous leg ulcer >2 cm	1. Betadine® and Jelonet® 2. Hydrocolloid dressing (biofilm)	Time to complete healing, pain and cost	Patients divided in two ulcer groups: 2–4 cm and >4 cm
Tarvainen[19]	1. Sealed envelope 2. 8 weeks 3. 14/13 4. Outpatient 5. 1 6. Finland 7. None reported	1. 67.7 in the iodine group/68.8 in the control 2. Patients with chronic leg ulcers	1. Cadexomer iodine 2. Dextranomer	Clinical response, adverse events and healing	
Vogt *et al.*[8]	1. Block randomisation 2. 13 days 3. 21/14 4. Hospital 5. 1 6. Germany 7. None reported	1. Not reported 2. Patients with wounds receiving meshed transplants	1. PVP-I hydrogel 2. Bactigras®	Epithelialisation, impedance, clinical evaluations of graft sites	
Vogt *et al.*[10]	1. Block randomisation 2. 20 days 3. 83/84 4. Hospital 5. 1 6. Germany 7. None reported	1. Not reported 2. Patients with wounds receiving meshed transplants	1. PVP-I hydrogel complex (Repithel®) 2. Jelonet®	Wound healing, graft take, bacterial load, and impedance	

[a] 1. Randomisation method. 2. Duration of follow-up. 3. No. of patients included per group (I_2/controls). 4. Setting. 5. No. of participating centres. 6. Country. 7. Source of funding.
[b] 1. Age (I_2/controls). 2. Type of wound.
[c] 1. Type of iodine dressing. 2. Type of control dressing.

treatments were used as comparator. Individual trial results for this type of wound are presented in Table S2. Vote counting of the overall trial results is presented in Tables S2 and II.

Primary outcomes

Bacterial load and wound infections. Groenewald *et al.* reported on bacterial cultures only in a qualitative way.[12] Moss *et al.* reported on bacterial load, graded semiquantitatively (0, +, ++, +++).[21] This was reported at the beginning and after six weeks of treatment for β-haemolytic *Streptococcus*, *Staphylococcus aureus*, *Pseudomonas*, and *Proteus*. No changes in bacterial load could be found in either treatment group.

Skog *et al.* reported on bacteriology but the proportion of patients per treatment group with an initial infection was unclear, so we could not estimate any treatment effect on bacteriology.[22]

Wound healing. In nine trials comparing 11 wound care products this outcome was reported (Table S2). Two trials found a significant

Table II
Vote-counting table summarising the effects of iodine on different outcome parameters according to wound types

Outcome	In favour of iodine	Indifferent	In favour of control	Total
Chronic ulcers (12 trials)				
Bacterial load		1		1
Complete wound healing	7	1	3	11
Reduction in wound surface	6		2	8
Pain	2		6	8
Increased ulcer size	2			2
Erosions/ulcerations/irritation/ erythema/(allergic) dermatitis	3		4	7
Thyroid hormone levels		1		1
Serum iodine levels			2	2
Costs	1		2	3
Total	21	3	19	43
Pressure ulcers (3 trials)				
Infection			2	2
Complete wound healing		1		1
Reduction in wound surface	3			3
Wound ready for surgical closure			2	2
Pain	1			1
Erosions/ulcerations/irritation/ erythema/(allergic) dermatitis			1	1
Total	4	1	5	10
Acute wounds (7 trials)				
Infections occurring		1	3	4
Infections cured	1		1	2
Complete wound healing	3	1	1	5
Wound granulation			1	1
Pain	1		1	2
Hypergranulation	1			1
Erosions/ulcerations/irritation/ erythema/(allergic) dermatitis	1		2	3
Hospital stay			1	1
Total	7	2	10	19
Burn wounds (3 trials)				
Complete wound healing	3			3
Pain	1			1
Erosions/ulcerations/irritation/ erythema/(allergic) dermatitis			1	1
Total	4	0	1	5
Skin grafts (4 publications on 2 trials)				
Infection	1			1
Complete wound healing	1			1
Reduction in wound surface	1			1
Graft loss	2			2
Thyroid hormone levels		2		2
Total	5	2	0	7
Overall totals	41[a]	8	35	84

Numbers represent the numbers of studies that give results on the respective outcome.
[a] $P = 0.031$ (McNemar test).

difference in favour of (cadexomer) iodine over local best practice, zinc paste, saline gauzes, and Gentian Violet.[11,13] The results of one trial favoured Debrisan® over iodine.[11] Six trials found no significant differences.

Six studies comparing seven wound care products used reduction in wound surface as surrogate endpoint for wound healing.[13,16–18,20,21] Cadexomer iodine resulted in a quicker wound size reduction than paraffin gauze or dextranomer.[16,17] However, no significant differences in reduction speed were observed between iodine and hydrocolloids or zinc paste.[13,16] Three studies did not give standard deviations in their results.[18,20,21]

Secondary endpoints
Adverse events. Seven trials reported on adverse effects: erosions or ulcerations, pain, dermatitis and allergic reactions, effect on serum iodine levels, and patient withdrawals because of increased ulcer size.

Hanson *et al.* reported on serum iodine levels.[16] However, we could not compare these serum levels to known reference values in the literature to assess their (ab)normality. The total number of patients and time of measurement was not stated, so we could not calculate any *P*-values. Holloway *et al.* reported no significant changes in thyroid functions in either treatment group.[20]

Two studies reported on the number of patients experiencing pain on application of cadexomer iodine.[13,22] Although the individual study results showed an insignificant trend, the pooled data showed an RD of 0.10 (95% CI: 0.01–0.19), to the detriment of iodine. Smith *et al.* found significantly more pain during the first month of treatment with iodine in ulcers smaller than 4 cm, but not in larger ulcers.[18]

Ormiston *et al.* found significantly more eczema, stinging, itching or rashes in patients treated with iodine, whereas Tarvainen *et al.* found no difference in erythema, oedema, stinging, or pain.[17,19]

Overall, out of the 20 outcome comparisons in these seven trials addressing adverse effects of iodine versus another wound dressing or topical agent, five showed a significant difference in favour of iodine and four against iodine (Table S2). These adverse events were all reversible, without serious sequels. Nine comparisons showed no significant difference, and two could not be assessed due to missing data.

Costs. Two trials reported on costs. Apelqvist *et al.* calculated the costs on a weekly basis and allocated these to staff, transportation, material, drugs, and total weekly costs.[14] The mean total weekly costs were: (US)$111 (65–210) for iodine vs 175 (53–331) for the control group. No standard deviations were given for any of the cost calculations. The authors also calculated weekly costs per patient healed: $379 for iodine vs $1579 for the control group, receiving gentamicin solution, streptodornase, or saline gauzes.[23]

Hanson *et al.* reported on material costs and the mean number of dressing changes per week, so we could recalculate the material costs per day.[16] These were $3.00 for cadexomer iodine paste, $0.65 for hydrocolloid gauze dressings, and $0.09 for paraffin gauze dressings.

Pressure ulcers

Three trials reported on patients with pressure ulcers.[23–25] Individual trial results for this type of wound are presented in Table S3. Vote counting of the overall trial results is presented in Tables S3 and II.

Primary endpoints
Bacterial load and wound infections. Kucan *et al.* reported the number of patients who reached a bacterial count $<10^5$ per gram of tissue during the three-week treatment period. Seven patients ($N = 11$) in the iodine group compared with 11 ($N = 14$) in the saline group and 15 ($N = 15$) in the silver group reached this endpoint.[25]

Wound healing. All three studies reported on wound healing, but by means of different outcome parameters, e.g. time to complete wound healing, wound size reduction or readiness for surgical closure.[23–25] In these studies, three wound healing outcomes were significantly in favour of povidone or cadexomer iodine; while two were it was in favour of other debriding or antiseptic agents or dressings.

Secondary endpoints
Adverse events. Only one trial has reported on pain and other adverse effects.[24] No significant differences were found in pain

scores, but significantly more mild adverse effects were found in the cadexomer iodine group than in those treated with debriding agents, saline or non-adhesive dressings.

Acute wounds

Seven studies reported on patients with acute wounds.[26–32] Individual trial results for this type of wound are presented in Table S4. Vote counting of the overall trial results is presented in Tables S4 and II.

Primary endpoints

Bacterial load and infection. Five studies reported on bacterial load and infection rates.[26–30] Al-Waili *et al.* found a nine-day longer time to reach a negative culture with iodine plus ethanol than with honey in gynaecological surgery wounds. In one study involving emergency hand surgery, Rifamycin SV MMX® prevented post-operative infection better than povidone iodine.[26,27] Another study found no significant differences as to infection prevention by iodine after appendicectomy, and the study by Dovison in nail surgery showed no differential protective effect of iodine, paraffin gauze or Intrasite® gel.[29,30] No differences were found between povidone iodine and a silver-containing hydrofibre to cure open wound infections.[28]

Wound healing. Five trials reported some measurement of wound healing. Four trials reported on the number of days until complete wound healing. With povidone iodine, nail wounds healed 7 days quicker than with Release®, but no significant difference was found as compared with paraffin gauze or Intrasite gel.[31] In wounds after gynaecological surgery, iodine plus alcohol resulted in an 11 day slower healing than honey.[28] In open surgical wounds no significant differences were observed.[28] In another study no differences were seen in wound granulation improvement.[32]

Secondary endpoints

Adverse events. Iodine was found to cause significantly less hypergranulation than Intrasite gel, but more trauma to the wound than a silver-containing hydrofibre.[28,30] Hospital stay was found to be significantly longer when iodine plus alcohol was used than with honey.[26] No significant differences in skin reactions were found.[28] Pain scores could not be analysed due to missing standard deviations.[28,29]

Burn wounds

Three studies reported on patients with burn wounds.[33–35] Individual trial results for this type of wound are presented in Table S5. Vote counting of the overall trial results is presented in Tables S5 and II.

Primary endpoints

Bacterial load and infection. One trial reported a similar number of patients with a positive wound culture between Inadine™ and Bactigras®, but it was unclear when the wound swabs were obtained.[33]

Wound healing. One trial showed a significantly (two days) quicker wound healing with povidone iodine-impregnated gauze than with a chlorhexidine-impregnated gauze.[33] Such a difference was also found in another trial comparing povidone iodine with silver sulfadiazine.[34] Another (large) trial reported that significantly more patients were healed within six weeks with iodine plus neosporin than with silver sulfadiazine.[35] It is unclear whether healing was due to iodine; neosporin, or both.

Secondary endpoints

Adverse events. Pain during dressing removal did not differ significantly between povidone iodine-impregnated gauzes and chlorhexidine-impregnated gauzes.[33] Nor did adverse event rates differ between povidone iodine and silver sulfadiazine.[34]

Skin grafts

Four studies reported on patients with skin grafts[7–10]: Hauser *et al.* and Vogt *et al.*[8] used the same patient sets, as did Reimer *et al.* and Vogt *et al.*[10] We therefore only report the data of Vogt *et al.*[8,10] Individual trial results for this type of wound are presented in Table S6. Vote counting of the overall trial results is presented in Tables S6 and II.

Primary endpoints

Bacterial load and infection. One trial showed no significant difference in infection rates between povidone iodine and paraffin gauze.[10]

Wound healing. Three trials reported wound healing. In one trial povidone iodine resulted in a (three days) quicker wound healing than paraffin gauze,[10] whereas two trials showed significantly less graft loss when using povidone iodine than with paraffin gauze with or without chlorhexidine.[8,9]

Secondary endpoints

Adverse events. One trial reported no adverse events and T_3 and T_4 levels remained within the normal range.[8] Vogt *et al.* also reported normal T_3 and T_4 levels.[10]

Discussion

Iodine has been used as an antiseptic for more than a century. Despite its reputation, this systematic review yielded only 27 randomised trials conducted since 1976 on the effectiveness of various iodine-containing products to treat or prevent infection in wound care. To date, however, iodine is one of the best-documented antiseptic agents. The majority of trials showed no substantial differences in beneficial or adverse reactions between iodine and other methods of local care for various chronic and acute wound types. Most of these studies used povidone or cadexomer iodine and the results did not differ among the various wound types.

A few trials did show a difference. In these studies, iodine was found superior to non-antiseptic dressings (paraffin dressings, dextranomer, zinc paste), and other antiseptic agents (such as silver sulfadiazine cream or chlorhexidine dressings), but inferior to a local antibiotic (Rifamycin®) or, when combined with alcohol, to crude honey, in reducing bacterial count and/or wound size. This seeming inferiority to honey may well be due to the addition of 70% alcohol, which can be cytotoxic.[26] Another trial comparing povidone iodine with honey did not show this effect.[36] Recently introduced antiseptic agents, such as polyhexamethylene biguanide, are now being evaluated against iodine products.[37–39]

In three trials, no harmful effect of iodine on thyroid function was observed, as opposed to initial alarming reports about this risk, particularly in premature neonates.[40] Also, no major adverse effects were seen with iodine regarding allergic responses or cytotoxicity, inasmuch as it did not reduce wound healing speed, which has been a longstanding opinion.[4] As it seems that iodine has no (dis) advantages compared with other products, the overall cost could eventually be the deciding factor for rejecting or accepting the use of iodine in the treatment of wounds.

One of the limitations of this review is the fact that many RCTs were more than 10 years old. Several of the trials predate the publication of the CONSORT statement. Hence, they were not

performed or described according to present-day standards. This makes the interpretation of the methodology of the trials difficult and may have caused bias, one being the finding that the results of most trials were in favour of the experimental rather than the control treatment used (Table S7).[41] Also, relatively few direct comparisons between iodine and another antiseptic agent were available.

Second, this review does not offer evidence for other clinically relevant questions about the effectiveness of iodine to prevent wound infection, the optimum method of administration (for example in the form of povidone, cadexomer or liposome), or the antiseptic of choice for particular (e.g. pseudomonas) infections or wound types. These questions deserve further and proper investigation.

Third, interpretation of trial results by means of vote counting when meta-analyses are not possible is under debate as it does not take into account study size or effect size. On the other hand, appreciating only the statistically significant results may also be biased by the usually underpowered study sizes, the high number of outcomes analysed, and by publication of the significant results only. Hence, we have presented both in an attempt to summarise the available data as objectively as possible.

Fourth, the evaluation of severe adverse effects, if any, may not have become clear from RCTs, as they are not the appropriate study design for this purpose. Cohort or case–control studies, if available, might shed more light on this, but were excluded here to present evidence with the least risk of bias.

Despite its long history, the use of iodine in wound treatment is still defendable because the best available evidence supports neither the purported harmful effects nor a delay of the wound-healing process, particularly in chronic and burn wounds. In addition, the effects of iodine are the best documented among the presently available antiseptic agents. Given the increasing microbial resistance against antibiotics, clinicians should rely more heavily on the use of local antiseptic therapies instead of (local) antibiotics if an indication for the use of antimicrobials is present.

There is a need for high quality RCTs addressing the effectiveness of iodine to treat or prevent wound infection, in order to clearly determine the place of iodine in present-day wound care. With the increasing cost of healthcare, future studies should also incorporate the cost-effectiveness of antiseptics.

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Conflict of interest statement
None declared.

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Appendix. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.jhin.2010.04.026.

References

1. Abraham GE. The history of iodine in medicine. Part 1: from discovery to essentiality. *Orig Internist* 2006;**13**:29–36.
2. Lineaweaver W, Howard R, Soucy D, *et al*. Topical antimicrobial toxicity. *Arch Surg* 1985;**120**:267–270.
3. Brånemark PI, Albrektsson B, Lindström J, Lundborg G. Local tissue effects of wound disinfectants. *Acta Chir Scand* 1966;**357**(Suppl.):166–176.
4. Rodeheaver G, Bellamy W, Kody M, *et al*. Bactericidal activity and toxicity of iodine-containing solutions in wounds. *Arch Surg* 1982;**117**:181–186.
5. Banwell H. What is the evidence for tissue regeneration impairment when using a formulation of PVP-I antiseptic on open wounds? *Dermatology* 2006;**212**(Suppl. 1):66–76.
6. Goldenheim PD. An appraisal of povidone-iodine and wound healing. *Postgrad Med J* 1993;**69**(Suppl. 3):97–105.
7. Reimer K, Vogt PM, Broegmann B, *et al*. An innovative topical drug formulation for wound healing and infection treatment: in vitro and in vivo investigations of a povidone-iodine liposome hydrogel. *Dermatology* 2000;**201**:235–241.
8. Vogt PM, Hauser J, Rossbach O, *et al*. Polyvinyl pyrrolidone-iodine liposome hydrogel improves epithelialization by combining moisture and antisepsis. A new concept in wound therapy. *Wound Repair Regen* 2001;**9**:116–122.
9. Hauser J, Rossbach O, Vogt PM, *et al*. Efficacy of treatment with Repithel and Jelonet in comparison to treatment with Jelonet alone – a randomized clinical trial in patients receiving meshed skin grafts. *Zentralbl Chir* 2006;**131**:315–321.
10. Vogt PM, Reimer K, Hauser J, *et al*. PVP-iodine in hydrosomes and hydrogel – a novel concept in wound therapy leads to enhanced epithelialization and reduced loss of skin grafts. *Burns* 2006;**32**:698–705.
11. Altman MA, Richter IH, Kaplan LH. Use of an aqueous triple iodine solution in the treatment of chronic leg ulcers and gangrene. *Angiology* 1976;**27**:181–187.
12. Groenewald JH. An evaluation of dextranomer as a cleansing agent in the treatment of the post-phlebitic stasis ulcer. *S Afr Med J* 1980;**57**:809–815.
13. Laudanska H, Gustavson B. In-patient treatment of chronic varicose venous ulcers. A randomized trial of cadexomer iodine versus standard dressings. *J Int Med Res* 1988;**16**:428–435.
14. Apelqvist J, Ragnarson Tennvall G. Cavity foot ulcers in diabetic patients: a comparative study of cadexomer iodine ointment and standard treatment. An economic analysis alongside a clinical trial. *Acta Dermat Venereol* 1996;**76**:231–235.
15. Daróczy J. Quality control in chronic wound management: the role of local povidone-iodine (Betadine) therapy. *Dermatology* 2006;**212**(Suppl. 1):82–87.
16. Hansson C. The effects of cadexomer iodine paste in the treatment of venous leg ulcers compared with hydrocolloid dressing and paraffin gauze dressing. Cadexomer Iodine Study Group. *Int J Dermatol* 1998;**37**:390–396.
17. Ormiston MC, Seymour MT, Venn GE, Cohen RI, Fox JA. Controlled trial of Iodosorb in chronic venous ulcers. *Br Med J (Clin Res Ed)* 1985;**291**:308–310.
18. Smith JM, Dore CJ, Charlett A, Lewis JD. A randomized trial of biofilm dressing for venous leg ulcers. *Phlebology* 1992;**7**:108–113.
19. Tarvainen K. Cadexomer iodine (Iodosorb) compared with dextranomer (Debrisan) in the treatment of chronic leg ulcers. *Acta Chir Scand* 1988;**544** (Suppl.):57–59.
20. Holloway GA, Johansen KH, Barnes RW, Pierce GE. Multicenter trial of cadexomer iodine to treat venous stasis ulcer. *West J Med* 1989;**151**:35–38.
21. Moss C, Taylor AE, Shuster S. Comparison of cadexomer iodine and dextranomer for chronic venous ulcers. *Clin Exp Dermatol* 1987;**12**:413–418.
22. Skog E, Arnesjo B, Troeng T, *et al*. A randomized trial comparing cadexomer iodine and standard treatment in the out-patient management of chronic venous ulcers. *Br J Dermatol* 1983;**109**:77–83.
23. Kaya AZ, Turani N, Akyuz M. The effectiveness of a hydrogel dressing compared with standard management of pressure ulcers. *J Wound Care* 2005;**14**:42–44.
24. Moberg S, Hoffman L, Grennert ML, Holst A. A randomized trial of cadexomer iodine in decubitus ulcers. *J Am Geriat Soc* 1983;**31**:462–465.
25. Kucan JO, Robson MC, Heggers JP, Ko F. Comparison of silver sulfadiazine, povidone-iodine and physiologic saline in the treatment of chronic pressure ulcers. *J Am Geriat Soc* 1981;**29**:232–235.
26. Al-Waili NS, Saloom KY. Effects of topical honey on post-operative wound infections due to gram positive and gram negative bacteria following caesarean sections and hysterectomies. *Eur J Med Res* 1999;**4**:126–130.
27. Iselin F, Audren JL, Gouet O, Hautefort E, Peze W, Pradet G. Comparative study of the effects of a local antibiotic and a local antiseptic in emergency hand surgery. *Ann Chir Main Memb Super* 1990;**9**:65–71.
28. Jurczak F, Dugre T, Johnstone A, Offori T, Vujovic Z, Hollander D, on behalf of the AQUACEL Ag Surgical/Trauma Wound Study Group. Randomised clinical trial of Hydrofiber dressing with silver versus povidone-iodine gauze in the management of open surgical and traumatic wounds. *Int Wound J* 2007;**4**:66–76.
29. McGreal GT, Joy A, Manning B, *et al*. Antiseptic wick: does it reduce the incidence of wound infection following appendectomy? *World J Surg* 2002;**26**:631–634.
30. Dovison R, Keenan AM. Wound healing and infection in nail matrix phenolization wounds. Does topical medication make a difference? *J Am Podiatr Med Assoc* 2001;**91**:230–233.
31. Denning L. The effect iodine has on post-phenolised nail surgery wounds. *Br J Podiatry* 2003;**6**:96–99.
32. Michiels I, Christiaens MR. Dextranomer (Debrisan) paste in post-operative wounds. A controlled study. *Clin Trials J* 1990;**27**:283–290.
33. Han KH, Maitra AK. Management of partial skin thickness burn wounds with Inadine dressings. *Burns* 1989;**15**:399–402.

34. Homann HH, Rosbach O, Moll W, *et al*. A liposome hydrogel with polyvinylpyrrolidone iodine in the local treatment of partial-thickness burn wounds. *Ann Plast Surg* 2007;**59**:423–427.
35. Sinha R, Agarwal RK, Agarwal M. Povidone iodine plus neosporin in superficial burns – a continuing study. *Burns* 1997;**23**:626–628.
36. Marshall C, Queen J, Manjooran J. Honey vs povidine iodine following toenail surgery. *Wounds UK* 2005;**1**:10–18.
37. Hansmann F, Kramer A, Ohgke H, Strobel H, Müller M, Geerling G. Lavasept as an alternative to PVP-iodine as a preoperative antiseptic in ophthalmic surgery. Randomized, controlled, prospective double-blind trial. *Ophthalmologe* 2005;**102**:1043–1046. 1048–1050.
38. Motta GJ, Milne CT, Corbett LQ. Impact of antimicrobial gauze on bacterial colonies in wounds that require packing. *Ostomy Wound Manage* 2004;**50**:48–62.
39. Salas Campos L, Gomez Ferrero O, Estudillo Perez V, Fernandez Mansilla M. Preventing nosocomial infections. Dressings soaked in polyhexamethylene biguanide (PHMB). *Rev Enferm* 2006;**29**:43–48.
40. Smerdely P, Lim A, Boyages SC, *et al*. Topical iodine-containing antiseptics and neonatal hypothyroidism in very-low-birthweight infants. *Lancet* 1989;**2** (8664):661–664.
41. Moher D, Schulz KF, Altman DG, for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;**357**(9263):1191–1194.