Use of systemic antibiotics and antiseptics for venous leg ulcers

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Venous leg ulcers are a type of chronic wound that affects up to 1% of adults in developed countries during their lives. These wounds can be slow to heal – from a few weeks to more than 10 years – and, in some cases, never do so. They are usually associated with significant cost to patients and healthcare systems.

The main strategies to treat venous ulcers are compression therapy, primary wound contact dressings and antimicrobial therapy when the wound is thought to be infected. Two main approaches to manage clinical infection in venous leg ulcers are:

- Systemic and topical antibiotics
- Antiseptics.

A systematic review was undertaken to determine the effects of antibiotics and antiseptics on venous ulcers.

Review process

The review involved 45 randomised controlled trials with a total of 4,486 participants, from which 53 comparisons were reported. Five RCTs reported eight comparisons of systemic antibiotics and the remaining studies compared topical preparations: cadexomer iodine, povidone-iodine, peroxide-based preparations, honey-based preparations, silver-based preparations, topical antibiotics and other topical antiseptics.

Participants could be treated in any care setting and were those presenting with venous leg ulcers, as defined by the study author, or various wounds if the venous-ulcer results were reported distinctly. The intervention arm included antibiotics (topical or systemic, oral or intravenous) and topical antiseptics. No specifications on strength or duration were noted. The comparison arm was either a placebo, an alternate antibiotic or antiseptic, any other therapy, usual care or no treatment.

The primary outcome was wound healing, which could be measured as time to complete wound healing, proportion of wounds healed during follow-up, and changes in wound size when compared with size at baseline. Secondary outcomes were changes in signs and symptoms of clinical infection, changes in bacterial flora, development of bacterial resistance, ulcer recurrence rates, adverse events, participant satisfaction and health-related quality of life, and costs.

Of the studies, three had low risk of bias, one on honey-based preparations and two on silver-based preparations. 13 high risk of bias and 29 were at an unclear risk of bias. Meta-analysis was done where possible.

Findings

Systemic antibiotics

Five studies involving a total of 233 participants looked at systemic antibiotics.

Many treatments are used to treat infected venous leg ulcers but not all are effective.
They found the following:

- Comparing co-trimoxazole, gentamicin or amikacin with standard care showed no significant difference in healing (one study);
- Ciprofloxacin versus standard care or placebo demonstrated no difference in complete healing at 3-4 months (two studies);
- Ciprofloxacin versus trimethoprim showed no significant difference in healing (one study);
- Trimethoprim versus placebo showed no significant difference in healing (one study);
- Amoxicillin versus topical povidone-iodine showed no difference between groups in complete healing (one study).

The limited data suggested recurrence of ulcer infection was lower for povidone-iodine;

- All ulcers treated with levamisole healed compared with 76% in the placebo group (one study). The review says this trial was small, so the effect could have occurred by chance. Three patients reported gastric adverse events.

Topical antibiotics and antiseptics

Cadoxomer iodine. The evidence on cadoxomer iodine came from 11 RCTs with 922 participants; seven trials compared it with standard care. Data from four RCTs were pooled for the outcome of complete healing at 4-12 weeks, indicating 33% healed when given cadoxomer iodine and 15% healed on standard care. No differences in healing were found when cadoxomer iodine was compared with hydrocolloid dressings (one trial) paraffin gauze dressings (one trial), dextranomer (two trials) or silver-impregnated dressings (one trial).

Povidone-iodine. This was studied in six RCTs (639 participants). When compared with dextranomer in one trial, the mean time to healing was shorter in the dextranomer group (4.4 weeks versus 5.3 weeks) as was time to eradication of Staphylococcus aureus (14.7 days versus 18.7 days). However, this data should be interpreted with caution as the analysis method used by the trial authors was deemed inappropriate.

When povidone-iodine was compared with growth factor (one RCT) and hydrocolloid dressings (three trials), there was no difference in healing between treatment groups. When one trial compared it with a non-adherent paraffin-gauze dressing, there was a statistically significant difference in ulcer-area reduction at three months in favour of hyaluronic acid/povidone-iodine dressing. There was no difference in healing between treatment groups in one trial comparing moist or foam dressings with povidone-iodine. Two RCTs reported lower costs associated with povidone-iodine but a full economic analysis was not presented for either trial.

Peroxide-based preparations. Four trials (72 participants) tested peroxide-based preparations. Benzoyl peroxide 10% and 20% was significantly more effective than saline in terms of ulcer area remaining (one trial each). Hydrogen peroxide 1% cream compared with placebo resulted in significantly greater wound-area reduction (two trials).

Honey-based preparations. These were the subject of two multicentre RCTs with 476 participants. The first found no difference in complete healing when the preparations were compared with hydrogels; the second compared them with non-honey impregnated dressings and found no difference in time to healing and change in health-related quality of life.

Silver-based preparations. A total of 12 RCTs with 1,514 participants, making 13 comparisons, provided evidence on creams and dressings containing silver. No differences were found between treatment groups when silver sulphadiazine cream was compared with usual care (one trial), placebo (one trial), non-adherent dressings (one trial) or growth factor (one trial). Comparison between different silver-impregnated dressings found no difference between groups (one trial); a further eight trials found no difference between silver-impregnated and non-antimicrobial dressings.

Other topical antibiotics and antiseptics. Five RCTs (590 participants) provided evidence on other topical antibiotics and antiseptics. For topical antibiotics, one RCT suggested an increase in the proportion healed at four weeks when patients were treated with enzymatic cleaner compared with chloramphenicol-containing ointment. No differences were found between groups in complete healing for: framycetin sulphate ointment and enzymatic cleaner; chloramphenicol ointment and framycetin sulphate ointment; mupirocin ointment and vehicle; and topical antibiotics given according to antibiotic (in vitro testing) and herbal ointment. For topical antiseptics, data from one RCT suggested ulcers would present a better response (20% area reduction) when treated with an antiseptic ointment, ethacridine lactase compared with a placebo. No statistically significant difference was found between wounds treated with chlorhexidine solution and usual care in terms of time to healing.

Adverse events

More participants reported adverse events for cadoxomer iodine relative to standard care. Severe irritations were associated with benzoyl peroxide; more frequent adverse events were reported relative to honey-based preparations.

Conclusion

The studies did have some limitations: many were small and most were at high or unclear risk of bias. The review concludes:

- Evidence from RCTs of participants with infected wounds is sparse;
- It is difficult to interpret the effects of antibiotics and antiseptics on healing and infection;
- No evidence is available to support the routine use of systemic antibiotics to promote healing venous leg ulcers;
- The lack of reliable evidence means it is not possible to recommend the discontinuation of any of the agents;
- Levamisole was the only systemic antibiotic with evidence of benefit in terms of ulcer healing;
- Some evidence supports the use of cadoxomer iodine as a topical preparation but it was linked to more adverse events than usual care;
- Evidence does not support using honey- or silver-based preparations;
- The increase of bacterial resistance to antibiotics means these are only recommended in cases of clinical infection, not bacterial colonisation.

RECOMMENDATIONS

- Do not routinely use systemic antibiotics
- Do not discontinue use of any of the agents
- Cadexomer iodine can be used but has been associated with more adverse events than usual care
- Do not use honey- and silver-based preparations
- Antibiotics are recommended only in cases of clinical infection, not in bacterial colonisation.