

WHAT IS ALREADY KNOWN ON THIS TOPIC

Combined oestrogen and progestogen hormone replacement therapy initiated many years after menopause in asymptomatic women reduces fracture risk but increases thromboembolic, breast cancer, and possibly cerebrovascular risk

Oestrogen only hormone replacement therapy started near the menopause may decrease the risk of coronary heart disease, breast cancer, diabetes, and osteoporotic fractures

WHAT THIS STUDY ADDS

This study confirms an early increase in thromboembolic and cardiovascular risk in women starting hormone replacement therapy at a mean of 63 years and 15 years after the menopause

These uncommon serious events must be weighed against more common improvements in quality of life

These results cannot be applied to symptomatic women starting hormone replacement therapy near menopause, for whom cardiovascular benefits have recently been described

Zealand monitored local progress and received reports on progress from the UK steering committee. The principal investigators from Australia and New Zealand were non-voting members of the UK steering committee.

Competing interests: WISDOM was run and funded independently of industry. The funding bodies had no influence on the results except for the early curtailment of the trial by the MRC. Wyeth Ayerst provided active drugs and matched placebo but had no other involvement in the trial. All authors have declared no direct conflicts of interest. AHM and BL have received research grants and lecture honoraria from a variety of industry sources not associated with WISDOM.

Ethical approval: UK approval was granted by the South Thames Regional Health Authority Multicentre Research Ethics Committees and by the relevant local research ethics committees. Australian approval was given by the human research ethics committees for the universities of Adelaide, Newcastle, and Monash and by the Royal Australian College of General Practitioners' National Research and Evaluation Ethics Committee. New Zealand approval was given by the Wellington Regional Ethics Committee and the Auckland and Canterbury ethics committees.

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Dressings for venous leg ulcers: systematic review and meta-analysis

Simon Palfreyman,¹ E Andrea Nelson,² Jonathan A Michaels¹

ABSTRACT

Objective To review the evidence of effectiveness of dressings applied to venous leg ulcers.

Design Systematic review and meta-analysis.

Data sources Hand searches of journals and searches of electronic databases, conference proceedings, and bibliographies up to April 2006; contacts with dressing manufacturers for unpublished studies.

Studies reviewed All randomised controlled trials that evaluated dressings applied to venous leg ulcers were eligible for inclusion. Data from eligible studies were extracted and summarised independently by two reviewers using a data extraction sheet. Methodological quality was assessed independently by two reviewers.

Results The search strategy identified 254 studies; 42 of these fulfilled the inclusion criteria. Hydrocolloids were no more effective than simple low adherent dressings used beneath compression (eight trials; relative risk for healing with hydrocolloid 1.02, 95% confidence interval 0.83 to 1.28). For other comparisons, insufficient

evidence was available to allow firm conclusions to be drawn. None of the dressing comparisons showed evidence that a particular class of dressing healed more ulcers. Some differences existed between dressings in terms of subjective outcome measures and ulcer healing rates. The results were not affected by the size or quality of trials or the unit of randomisation. Insufficient data were available to allow conclusions to be drawn about the relative cost effectiveness of different dressings. **Conclusions** The type of dressing applied beneath compression was not shown to affect ulcer healing. The results of the meta-analysis showed that applying hydrocolloid dressings beneath compression produced no benefit in terms of ulcer healing compared with applying simple low adherent dressings. No conclusive recommendations can be made as to which type of dressing is most cost effective. Decisions on which dressing to apply should be based on the local costs of dressings and the preferences of the practitioner or patient.

¹Sheffield Vascular Institute, Northern General Hospital, Sheffield S5 7AU

²School of Healthcare, University of Leeds, Leeds LS2 9UT

Correspondence to: SJ Palfreyman simon.palfreyman@sth.nhs.uk

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INTRODUCTION

Multilayer compression bandaging has been identified as the gold standard in the treatment of venous leg ulcers.¹⁻³ Dressings are usually placed over the ulcer before compression bandages or hosiery are applied, with the intention of promoting healing and preventing the bandages sticking to the wound. However, the evidence of any increased benefit provided by these dressings, which can contribute significantly to the cost of treating a venous leg ulcer, is less clear than for compression.

Large numbers of different wound dressings are available, but the evidence for their use is equivocal. Whether any particular dressing or type of dressing affects the healing of ulcers needs to be established. Many of these dressings are relatively expensive, with a difference of up to six times in unit cost between the more expensive and cheaper dressings.⁴

This study was based on a recently published Cochrane Collaboration review.⁵ We aimed to assess the effectiveness of wound dressings used in the treatment of venous leg ulcers.

METHODS

We sought to summarise all randomised controlled trials evaluating dressings in the treatment of venous leg ulcers. Two reviewers independently assessed trials for suitability; a third reviewer arbitrated any disagreements. We excluded trials that included patients with wounds such as arterial and diabetic ulcers. The primary outcome measure was time to complete ulcer healing or proportion of ulcers completely healed.

We identified randomised controlled trials by searching Medline, Embase, CINAHL, and the Cochrane Wounds Group specialised trials register up to April 2006. Search terms included venous ulcer, foot ulcer, skin ulcer, leg ulcer, varicose ulcer, dressing, gauze, hydrocolloid, alginat, hydrogel, foam, and film. We also examined conference proceedings. We placed no restrictions in terms of language or year of publication. We hand searched key journals, checked citations, and contacted experts in the field of wound care to enquire about ongoing and recently published trials.

Trials had to report time to complete ulcer healing, proportion of ulcers completely healed, or reduction in area; we excluded composite outcome measures. We assessed the quality of the trials on comparability of

treatment groups at baseline, analysis of outcomes on an intention to treat basis, completeness of follow-up, and blinding and objectivity of outcome assessors.

All analysis was on an intention to treat basis. We estimated the relative risk of healing for each study; where similar interventions were compared in similar populations, we then considered using meta-analysis to estimate an aggregate relative risk. We assessed clinical and statistical heterogeneity.

RESULTS

Of 254 citations initially identified, 44 studies were eligible for inclusion.^{w1-w44} We included 42 completed trials involving 3001 participants. Some trials used the limb or ulcer as the unit of randomisation; 3037 ulcers or limbs were included in the trials. Most (31/42, 74%) of the trials had 100 or fewer participants, and 36% (15/42) had fewer than 50 participants.

No inclusion criteria were reported for 38% of studies. Only 11 (26%) trials stated the method of randomisation.^{w3-w13} Most trials reported that the treatment groups were comparable at baseline. Most of the trials (31/42, 74%) reported the total number of ulcers healed during the trial. The remaining 26% (11/43) of trials used only the ulcer healing rate as an outcome measure. The duration of the trials ranged from four weeks to 48 weeks. The mean duration/follow-up was 14 weeks, and the median duration was eight weeks.

We used a random effects model to obtain aggregate outcomes for the relative risk of complete ulcer healing. The table shows the results of the meta-analysis.

Hydrocolloid dressings

Twenty seven trials evaluated hydrocolloid dressings.

Hydrocolloid versus low adherent dressings—Nine trials (928 participants) compared hydrocolloid and low adherent dressings.^{w4 w7 w9 w10 w14-w18} We excluded one trial from the meta-analysis.^{w17} The remaining eight trials included 792 people, and the pooled relative risk for healing with hydrocolloid was 1.02 (95% confidence interval 0.83 to 1.25) (fig 1). We detected significant heterogeneity within this comparison ($I^2=46.6\%$; $\chi^2=13.11$, $df=7$; $P=0.07$). Exclusion of one trial removed the statistical heterogeneity and did not affect the finding of no evidence of a difference in healing rate between hydrocolloids and simple low

Meta-analysis results

Comparison	No of trials (total No of participants)	Pooled relative risk (95% CI)
Hydrocolloid v low adherent	8 (792) (1 trial excluded ^{w17})	1.02 (0.83 to 1.25)
Hydrocolloid v foam	4 (311)	0.98 (0.79 to 1.22)
Hydrocolloid v alginate	3 (80)	0.72 (0.15 to 3.42)
Hydrocolloid v hydrocolloid	3 (98)	1.56 (0.67 to 3.63)
Foam v low adherent	2 (203) (1 trial excluded ^{w12})	1.35 (0.93 to 1.94)
Foam v foam	2 (136)	1.2 (0.77 to 1.87)
Hydrogel v low adherent	2 (151)	1.53 (0.96 to 2.42)
Hydrogel v hydrogel	2 (175)	NA

NA=not applicable.

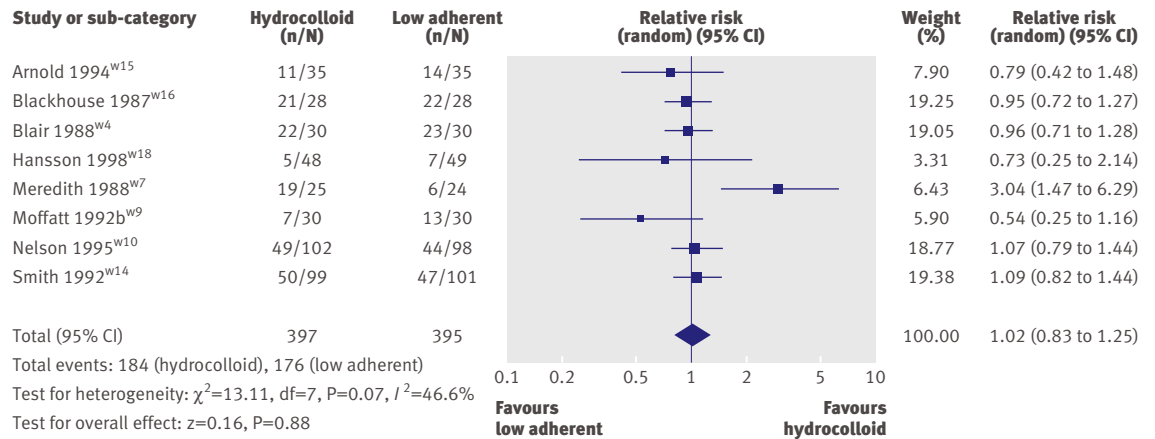


Fig 1 | Hydrocolloid dressings versus low adherent dressings

adherent dressings (relative risk=0.98, 0.85 to 1.12; $I^2=0\%$).^{w7}

Hydrocolloid versus foam dressings—Four trials (311 participants) reported the total number of ulcers healed at 12 weeks for hydrocolloid dressings compared with foam dressings.^{w5 w19-w21} Meta-analysis showed a pooled relative risk for healing of 0.98 (0.79 to 1.22) (fig 2), indicating no evidence of a statistically significant difference in healing rates. We detected no heterogeneity within the comparison ($I^2=0\%$; $\chi^2=0.07$, $df=3$, $P=0.97$).

Hydrocolloid versus alginate dressings—Two trials (80 participants) compared hydrocolloid dressings with alginate dressings.^{w22 w23} The pooled relative risk for ulcer healing for hydrocolloids compared with alginate dressings was 0.72 (0.48 to 1.69) at 6-13 weeks. We found high heterogeneity ($I^2=52\%$; $\chi^2=2.08$, $df=1$; $P=0.15$).

Hydrocolloid versus hydrocolloid—Three trials (98 participants) compared various hydrocolloid dressings.^{w24-w26} We could include only two in the meta-analysis, as one did not report the total number of ulcers healed.^{w26} The meta-analysis showed high heterogeneity ($I^2=69.7\%$; $\chi^2=3.3$, $df=1$; $P=0.07$) and no statistical difference between the dressings (relative risk=1.56, 0.67 to 3.63).

Hydrocolloid versus other dressings—Two trials (237 participants) compared hydrocolloid and hydrogel

dressings.^{w18 w27} The analysis was not intention to treat. The outcomes reported were percentage reduction in ulcer area at 28 days (44.6% hydrogel v 33.3% hydrocolloid) and the reduction of the ulcer surface area at 28 days (4.5 cm² hydrogel v 2.1 cm² hydrocolloid). One trial (28 participants) compared hydrocolloid and gauze.^{w28} It reported a relative reduction in ulcer area of 19% for the gauze group and 51% for the hydrocolloid group. No statistical analysis of the results was reported. One trial (93 participants with 98 ulcers) compared hydrocolloid dressing and a lyophilised collagen dressing.^{w29} The unit of randomisation was the ulcer and not the patient. No statistical differences between the dressings were reported. One trial (110 participants) compared hydrocolloid dressing (Varihesive E) and magnesium sulphate paste beneath a gauze dressing.^{w30} The trial reported three ulcers healed in the hydrocolloid group and no ulcers healed in the other group.

Foam dressings

Foam versus low adherent dressings—Three trials (253 participants) compared foam dressings with low adherent dressings.^{w12 w31 w32} One trial did not report the total number of ulcers healed and so could not be included

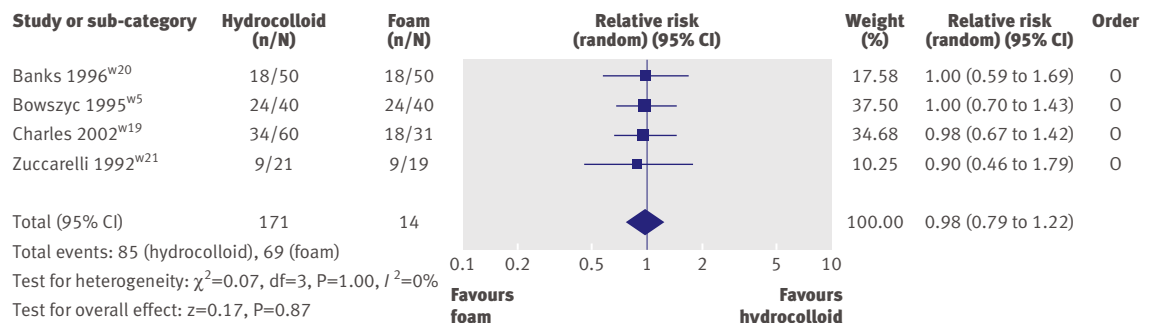


Fig 2 | Hydrocolloid dressings versus foam dressings

in the meta-analysis.^{w12} For the other two studies, the pooled relative risk was 1.35 (0.93 to 1.94), with no statistical heterogeneity ($I^2=0\%$; $\chi^2=0.0$, $df=1$; $P=0.99$).

Foam versus foam dressings—Two trials (136 participants) compared various foam dressings.^{w3 w33} The aggregate relative risk of healing for the two studies was 1.2 (0.77 to 1.87), with no statistical heterogeneity ($I^2=0\%$, $\chi^2=0.88$, $df=1$; $P=0.35$).

Foam versus alginate dressings—One trial (40 participants) compared foam dressings with alginate dressings.^{w34} No statistically significant difference was found between the dressings. The reported hazard ratio for healing was 1.75 (0.79 to 3.88).

Foam versus silicone dressings—One trial (156 participants) compared foam dressings against silicone dressings.^{w35} No statistically significant difference was found between the dressings. The reported hazard ratio for healing was 1.17 (0.79 to 1.72).

Hydrogel dressings

Two trials (151 participants) compared hydrogel dressings with low adherent dressings.^{w11 w36} The aggregate relative risk for healing with hydrogel compared with low adherent dressings was 1.53 (0.96 to 2.42; $I^2=0\%$, $\chi^2=0.07$, $df=1$; $P=0.79$).

Alginate dressings

Alginate versus low adherent dressings—One trial (60 participants) compared alginate with low adherent dressings.^{w39} It found no statistically significant difference between the two dressings.

Alginate versus alginate—One trial (20 participants) compared different alginate.^{w40} The study reported the total number of ulcers healed at eight weeks and found no statistically significant differences between the two. One trial (113 patients with 133 ulcerated limbs) compared alginate dressings.^{w41} The treatments were zinc oxide impregnated cotton bandage (Viscopaste, $n=43$), zinc oxide impregnated stockinet (Acoband, $n=44$), and alginate dressing (Kaltostat, $n=46$). The study reported the total number of limbs healed. These were 34/43 (86%) in the Viscopaste arm, 26/44 (66%) in the Acoband arm, and 26/46 (57%) in the alginate arm. The relative risk of healing with the zinc paste bandage compared with the alginate dressing was 0.82 (0.61 to 1.1).

DISCUSSION

The results from our meta-analysis showed no statistically significant difference in terms of total ulcers healed between any of the dressing types. One consideration when reviewing these results must be that an intention to treat perspective was used, which assumed that losses to follow-up failed to heal. This could have underestimated the healing rates.

Quality of included trials

Most of the trials included in this review had a small sample size (range 13-200, mean 76, median 70) and therefore had low power to detect clinically important

differences. This was a concern, as small trials are at a higher risk of publication bias than large trials. Although the results for healing in these trials were usually inconclusive, most trials were not inconclusive in their conclusions. Most of the trials in this review were funded by dressing manufacturers, and we cannot be certain whether unpublished trials exist, or if, in the published trials, outcome measures have been selectively reported. We also found problems in terms of reporting of trials. Only three studies stated the method of randomisation and blinding of allocation,^{w4 w10 w11} and only one reported blinding of assessment.^{w19}

The trials were of relatively short duration (range 4-48, mean 14, median 8 weeks). Venous ulcers usually take months to heal,⁶ so trials with short durations fail to capture most healing events, further eroding power to detect clinically important differences as statistically significant.

External validity of included trials

The external validity of many of these trials is threatened by the fact that they limited inclusion by ulcer size. Only one trial used life table analysis, summarising both how many people's ulcers healed and how quickly they healed.^{w9} Many studies used rate of reduction in ulcer area as an outcome measure; however, this is not necessarily a predictor of healing and can be misleading.⁷

Other outcome measures used included patient derived and nurse derived subjective measures such as "satisfaction" and pain. The use of subjective outcomes in trials can lead to bias, especially if the tools used are not tested for reliability and validity and if blinding to treatment allocation is not used.

Cost and quality of life data

Cost and quality of life data used in the studies were also generally poor quality or lacking. The inclusion of more sophisticated measures of quality of life when evaluating dressings is an area that needs to be tackled. This is particularly important as it may be one of the few ways to distinguish between dressings.

The poor reporting of cost data was a particular concern. Where such data were collected,^{w7 w14 w29} the reporting did not conform to rigorous guidelines for

WHAT IS ALREADY KNOWN ON THIS TOPIC

Dressings are applied over ulcers with a view to aiding healing and improving patients' comfort

A wide variety of brands and types of dressing are available, but the evidence for their effectiveness is equivocal

WHAT THIS STUDY ADDS

Insufficient evidence of effectiveness exists to recommend one type of dressing in preference to another

Hydrocolloid dressings offer no healing benefit compared with simple dressings under compression

In the absence of evidence for healing benefit, cost should be a factor in the choice of dressings

economic evaluations.⁸ The trials simply totalled the monetary cost of the dressings and did not examine their cost effectiveness.

Clinical implications

Although a wide variety of dressings are available, and used on venous leg ulcers, we found insufficient evidence to justify the use of a particular dressing or dressing type in preference to any other. In particular, the use of hydrocolloid dressings rather than simple, low adherent dressings should be questioned. Cost effectiveness studies examining dressings for venous leg ulcers are urgently needed, as dressing frequency drives costs by influencing the amount of time taken by clinicians to treat ulcers.

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Competing interests: A trial by EAN was included in the review.
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Provenance and peer review: Non-commissioned; externally peer reviewed.

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Sexual abstinence only programmes to prevent HIV infection in high income countries: systematic review

Kristen Underhill, Paul Montgomery, Don Operario

EDITORIAL by Hawes and colleagues

Centre for Evidence-Based Intervention, University of Oxford, Oxford OX1 2ER

Correspondence to: K Underhill
 kristen.underhill@socres.ox.ac.uk

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ABSTRACT

Objective To assess the effects of sexual abstinence only programmes for HIV prevention among participants in high income countries.

Design Systematic review.

Data sources 30 electronic databases without linguistic or geographical restrictions to February 2007, contacts with experts, hand searching, and cross referencing.

Review methods Two reviewers independently applied inclusion criteria and extracted data, resolving disagreements by consensus and referral to a third reviewer. Randomised and quasirandomised controlled trials of abstinence only programmes in any high income country were included. Programmes aimed to prevent HIV only or both pregnancy and HIV. Trials evaluated biological outcomes (incidence of HIV, sexually transmitted infection, pregnancy) or behavioural outcomes (incidence or frequency of unprotected vaginal, anal, or oral sex; incidence or frequency of any vaginal, anal, or oral sex; number of partners; condom use; sexual initiation).

Results The search identified 13 trials enrolling about 15 940 US youths. All outcomes were self reported. Compared with various controls, no programme affected incidence of unprotected vaginal sex, number of partners, condom use, or sexual initiation. One trial observed adverse effects at short term follow-up (sexually transmitted infections, frequency of sex) and long term follow-up (sexually transmitted infections, pregnancy) compared with usual care, but findings were offset by trials with non-significant results. Another trial observed a protective effect on incidence of vaginal sex compared

with usual care, but this was limited to short term follow-up and countered by trials with non-significant findings. Heterogeneity prevented meta-analysis.

Conclusion Programmes that exclusively encourage abstinence from sex do not seem to affect the risk of HIV infection in high income countries, as measured by self reported biological and behavioural outcomes.

INTRODUCTION

Programmes aimed at sexual abstinence only are one strategy for preventing sexually acquired HIV. These interventions encourage primary abstinence (delaying sexual debut) and secondary abstinence (returning to abstinence after sexual activity) whereas abstinence plus programmes promote abstinence along with safer sex strategies.

Abstinence only programmes to prevent HIV are more likely to acknowledge the HIV related risks of oral sex, anal sex, same sex sexual behaviours, and non-sexual means of transmission, whereas programmes to prevent pregnancy only may just mention vaginal sex. To complement a systematic review of abstinence based programmes in developing countries we systematically reviewed trials of abstinence only programmes to prevent HIV infection or HIV and pregnancy in high income countries.

METHODS

We included randomised and quasirandomised controlled trials of sexual abstinence only interventions for HIV prevention in high income economies (see

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