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Phototherapy for treating pressure ulcers (Review)

Chen C, Hou WH, Chan ESY, Yeh ML, Lo HLD

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[Intervention Review]

Phototherapy for treating pressure ulcers

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ABSTRACT

Background

A pressure ulcer is defined as "an area of localized injury to the skin and/or underlying tissue, usually over a bony prominence, as a result of pressure, or pressure in combination with shear". The use of phototherapy - that is, light (or laser) used as an adjuvant, non-surgical intervention, with the aim of having a therapeutic effect on healing - has increased recently.

Objectives

To determine the effects of phototherapy on the healing of pressure ulcers.

Search methods

In January 2014, we searched the Cochrane Wounds Group Specialised Register; The Cochrane Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE; Ovid EMBASE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); and EBSCO CINAHL. We did not restrict the search by language or publication date.

Selection criteria

Randomised controlled trials (RCTs) comparing the effects of phototherapy (in addition to standard treatment) with sham phototherapy (in addition to standard treatment), another type of phototherapy (in addition to standard treatment) or standard or conventional treatment alone.

Data collection and analysis

Two review authors assessed studies for relevance and design according to the selection criteria, extracted data and evaluated study quality. The authors made attempts to obtain missing data by contacting study authors. Disagreement was resolved by consensus and discussion with a third review author.

Main results

We identified seven RCTs involving 403 participants. All the trials were at unclear risk of bias. Trials compared the use of phototherapy with standard care only (six trials) or sham phototherapy (one trial). Only one of the trials included a third arm in which another type of phototherapy was applied. Overall, there was insufficient evidence to determine the relative effects of phototherapy for healing pressure ulcers. Time to complete healing was reported in three studies. Two studies showed the ultraviolet (UV) treated group had a shorter mean time to complete healing than the control group (mean difference -2.13 weeks (95% CI -3.53 to -0.72, P value 0.003)). One study reported that the laser group had a longer mean time to complete healing than the control group (mean difference 5.77 weeks; 95% CI -0.25 to 11.79). However, this result should be interpreted with caution, as these were small studies and the findings may have been due to chance. Three studies reported proportions of ulcers healed with a variety of results. One study reported a different outcome measure, and the other two studies had different treatment durations. These variations did not allow us to pool the studies and draw any conclusions as to whether phototherapy is effective or not. Adverse effects were reported in only two studies that compared phototherapy with control; the risk ratio for adverse events was imprecise. One study reported risk ratio (RR) 0.72 (95%CI 0.18 to 2.80). However, another study reported RR 0.89 (95% CI: 0.71 to 1.12) based on the number of events in each group, rather than the number of people with events. Among five studies reporting the rate of change in ulcer area, three studies found no statistically significant difference between the two groups. Pooling was not undertaken because of differences in outcome measures reported. The results were based on data from trials with unclear risk of bias for which generation of the randomisation sequence, concealment allocation and blinding of outcome assessors were unclear. No studies reported on quality of life, length of hospital stay, pain or cost.

Authors' conclusions

We are very uncertain as to the effects of phototherapy in treating pressure ulcers. The quality of evidence is very low due to the unclear risk of bias and small number of trials available for analysis. The possibility of benefit or harm of this treatment cannot be ruled out. Further research is recommended.

PLAIN LANGUAGE SUMMARY

Phototherapy for treating pressure ulcers

What are pressure ulcers?

Pressure ulcers (also called bed sores or pressure sores) are sores on the skin caused by constant pressure or friction. They usually affect people who are immobilised or find it difficult to move themselves, for example the elderly or paralysed. Pressure ulcers frequently occur on bony parts of the body, such as the heels and hips, and also on the coccyx (tail bone). Pressure ulcers do not always heal, and, if they do heal, healing can take a long time.

What is phototherapy?

Phototherapy is a treatment in which part of the body is exposed to daylight, a or light of a specific wavelength. It is used for treating a variety of diseases, and may involve lights and lasers. Phototherapy is used to treat pressure ulcers in the hope that it will reduce the time the ulcers take to heal.

The purpose of this review

This review tried to find out whether phototherapy treatment(s) given in addition to standard care (i.e. pressure relief, removal of dead tissue from the wound, infection control and application of dressings) improves healing times for pressure ulcers. Standard care plus phototherapy could be compared against standard care alone, or against standard care plus sham phototherapy, or against standard care plus another type of phototherapy.

Findings of this review

The review authors searched the medical literature up to 7 January 2014, and identified seven relevant medical trials, with a total of 403 participants. Six trials compared the use of phototherapy with standard care only; one trial compared it with standard care plus sham phototherapy. Only one trial included a third treatment group that investigated another type of phototherapy.

Two trials reported the time taken for pressure ulcers to heal completely, and these showed an improvement in healing time for people in the phototherapy group who received treatment with ultraviolet light. However, this result should be interpreted with caution, as these were small, poor quality trials, at unclear risk of bias (i.e. with potentially misleading results), and the findings may have been due

to chance. The other trials reported either conflicting results or various measures/time points among trials, which meant that we could not conclude whether or not phototherapy is effective for treating pressure ulcers. Two trials reported incidence of harmful (adverse) effects and noted no significant differences between the phototherapy and standard treatment groups. Four trials provided funding information, two from industry funding, the others from an institutional grant. No studies reported on quality of life, length of hospital stay, pain or cost.

This review identified only a few, small studies provided with insufficient evidence to support the use of phototherapy as a routine treatment for pressure ulcers. More trials will need to be conducted before it can be established whether this treatment works and is safe.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Phototherapy versus control for treating pressure ulcers

Patient or population: patients being treated for pressure ulcers
Settings: hospitals, nursing homes, outpatient settings
Intervention: phototherapy versus control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Phototherapy versus control				
Time to complete healing (weeks) (UV vs control) Scale from: 0 to complete healing	The mean time to complete healing (weeks) (UV vs control) in the control groups was **7.95 weeks**	The mean time to complete healing (weeks) (UV vs control) in the phototherapy groups was **2.13 lower** (3.53 to 0.72 lower)		32 (2 studies)	⊕◯◯◯ **very low**[1,2,3]	
Time to complete healing (weeks) (laser vs control) weeks. Scale from: 0 to complete healing.	The mean time to complete healing (weeks) (laser vs control) in the control groups was **6.83 weeks**	The mean time to complete healing (weeks) (laser vs control) in the intervention groups was **5.77 higher** (0.25 lower to 11.79 higher)		8 (1 study)	⊕◯◯◯ **very low**[1,2,3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: we are very uncertain about the estimate

[1] According to risk of bias analysis table, there is a concern about bias in this study.
[2] The interventions used in the studies were diverse, as were the participant groups, and stages of wounds.
[3] The results show both potential harm and benefit from the intervention, the low number of participants included in the studies and available for analysis should be noted along with the width of the confidence intervals.

BACKGROUND

Description of the condition

According to the European Pressure Ulcer Advisory Panel (EPUAP) and the National Pressure Ulcer Advisory Panel (NPUAP), a pressure ulcer is defined as "an area of localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear" (EPUAP-NPUAP 2009). The stages of pressure damage and ulceration have been characterised as follows:

- Stage 1: non-blanchable area of redness without epithelial loss;
- Stage 2: ulcer presents either as an intact, or ruptured, serum-filled blister, or as a partial loss of dermal tissue;
- Stage 3: full-thickness dermal loss not exposing muscle, tendon or bone;
- Stage 4: ulcer has extensive tissue loss sufficient to expose muscle, tendon or bone (EPUAP-NPUAP 2009).

Pressure ulcers occur most commonly on the hips, buttocks and heels of the elderly and immobile (Kroger 2009).

A national survey of pressure ulcers in the USA reported a prevalence of 14.8% across 365 acute hospitals (Amlung 2001). Another review of hospitals showed large variations in reported prevalences that ranged from 5.1% to 32.1% in the UK, and from 4.7% to 29.7% in the USA and Canada (Kaltenthaler 2001). A later epidemiological study in Europe, Canada and the USA described the reported prevalence of pressure ulcers in European hospitals as ranging from 8.3% to 23% (Vanderwee 2007). In the UK, the overall prevalence of pressure ulcers within care settings was 10.2%, with 59% of these being hospital-acquired pressure ulcers (Phillips 2009). Pressure ulcers result in delayed recovery, and can increase the duration of hospital stay, leading to higher treatment costs and an impaired quality of life. In the USA 1.7 million people annually develop a pressure ulcer, and their treatment was estimated to have cost USD 6.4 billion in 1994 and USD 8.5 billion in 1997 (Allman 1997). The cost increased to USD 11 billion in 2006 (Russo 2008). The costs of pressure ulcer treatment (prevention) for England were estimated as high as £755 million (West 1994). The daily cost of treating a pressure ulcer varies from £1,064 to £10,551, which resulted in the total cost in the UK is £1.4-£2.1 billion annually (Bennett 2004). The estimated cost of treating a pressure ulcer case increased from £1,214 to £ 14,108 in a later study (Dealey 2012).

A Dutch study found that costs associated with the care of pressure ulcers were the third highest after those for cancer and cardiovascular diseases (Health Council of the Netherlands 1999).

Description of the intervention

Phototherapy consists of exposure to daylight, or a specific wavelength of light; it is used for treating a variety of diseases. The use of light (or laser) as an adjuvant (additional) non-surgical intervention with the aim of helping healing has increased in recent times (Whinfield 2009). There are several terms that refer to light therapy, for example; phototherapy, low level laser therapy (LLLT), low power laser therapy (LPLT), low intensity laser therapy (LILT), cold laser, therapeutic laser, light emitting diode (LED), low reactive level laser, diode laser (Enwemeka 2005), and UV light.

Phototherapy regimens are potentially very diverse and involve numerous treatment variables such as:

- radiation wavelength (Peavy 2002);
- continuous versus pulsed wave technology (Ohshiro 1988);
- energy density (Ohshiro 1988);
- polarization (Đurović 2008).

Phototherapy can be used to treat a variety of medical conditions and is thought to: reduce the swelling and inflammation associated with acute injuries in superficial muscles or tendons; improve wound healing of slow-to-heal or non-healing wounds in soft tissues or tendons; enhance absorption of interstitial fluid (fluid outside cells) and increase lymphatic circulation and drainage to increase tissue regeneration (Hawkins 2007).

Pressure ulcers are treated using a multiple-intervention approach. Phototherapy is usually an adjuvant intervention used alongside standard pressure ulcer care. Standard care may vary depending on the setting and local practice, but will typically consist of the following elements: pressure relief, debridement (removal of dead tissue), infection control and wound dressing. Although in vivo studies have shown a positive effect of phototherapy on wound healing, its mode of action is still not completely understood (Coombe 2001; Smith 1991).

Some phototherapy-related adverse events have been reported, for example erythema (photo-toxic/photo-allergic redness), pruritus (itching), and reactivation of viral infection (e.g. herpes simplex virus). Some chronic adverse effects, such as photo-ageing or skin cancer, have also been reported (Laube 2001). However, overall, the rate of acute adverse events, and in particular the rate of severe adverse events, has been reported as being low (Martin 2007).

How the intervention might work

The treatment goals of phototherapy are to eradicate bacteria from the ulcer, remove slough (loose, dead tissue) (Burger 1985), and stimulate the growth of granulation tissue and epidermis (Freytes 1965). It has been suggested that phototherapy could accelerate wound healing through various mechanisms such as: acceleration of the inflammatory phase (Robinson 1994); enhancing prostaglandin secretion (Eaglstein 1975; Kert 1989); enhancing collagen synthesis (Karu 1989; Monstrey 2002); enhancing fibroblast division (Karu 1989); epithelisation of tissue (Herascu

2005); proliferation of various cells (AlGhamdi 2012); enhancing macrophage phagocytosis (Rochkind 1989); activation of the immune system (Enwemeka 1988); enhancing blood flow and vascular permeability (Greaves 1970; Horwitz 1999; Ramsay 1976); inactivating bacteria (High 1983); stimulating keratinocyte division and motility (Grossman 1998; Haas 1990); and enhancing adenosine-5'-triphosphate (ATP) synthesis (Karu 1995). ATP transports chemical energy within the cells for metabolism. Light (phototherapy) increases ATP synthesis and proton gradients, which lead to an increase in cellular activity. Moreover, phototherapy has been shown to stimulate the expression of multiple genes related to cellular migration, proliferation, and also to modulate the production of growth factors and cytokines (Peplow 2011; Zhang 2003).

Why it is important to do this review

Phototherapy, including low-level laser therapy (LLLT), has been proposed as a promising treatment option for open wounds. Mester was the first to document the biological effects of LLLT in case reports (Mester 1971). There are also sparse references in the recent literature to the use by physical therapists of ultraviolet (UV) light for wound healing. The existing literature concentrates on broad-spectrum UV light sources (Burger 1985; Freytes 1965). Since Wills 1983 published the first randomised controlled trial (RCT) on this topic, several RCTs have made further investigations (Dehlin 2003; Đurović 2008; Lucas 2003; Nussbaum 1994; Schubert 2001; Shojaei 2008). This is a timely opportunity to undertake a systematic review that summarises the existing evidence in order to inform practice, and identifies gaps in the research evidence to guide future research.

OBJECTIVES

To determine the effects of phototherapy on the healing of pressure ulcers.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) evaluating phototherapy in the treatment of pressure ulcers. Quasi-randomised trials or controlled clinical trials (CCTs) were not considered in this review.

Types of participants

People of any age with pressure ulcers of any stage in any care setting. Participants were the primary unit of analysis. We did not include studies that analysed per ulcer because of the potential interaction between ulcers in a patient.

Types of interventions

The primary intervention was any form of single or multi-wavelength phototherapy in combination with usual pressure ulcer management. Our review includes low level laser therapy (LLLT), low power laser therapy (LPLT), low intensity laser therapy (LILT), cold laser, therapeutic laser, light emitting diode (LED), low reactive level laser, diode laser (Enwemeka 2005), and UV light. Acceptable control interventions included no phototherapy (usual care alone), sham phototherapy (an inactivated light source (with standard care)), or another form of phototherapy (with standard care) that is distinct from the primary intervention.

Types of outcome measures

Primary outcomes

Wound healing as measured by:

- time to healing/rate of healing;
- number of wounds healed in a specified time period.

Adverse events.

Secondary outcomes

- Change in wound size or wound surface area.
- Quality of life.
- Length of hospital stay.
- Pain (as measured by a validated scale).
- Cost.

Search methods for identification of studies

Electronic searches

For this seventh update we searched the following databases to identify reports of relevant randomised clinical trials:

- The Cochrane Wounds Group Specialised Register (searched 7 January 2014);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2013, Issue 12);
- Ovid MEDLINE (1948 to November Week 3 2013);
- Ovid EMBASE (1980 to 2014 Week 01);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations 7 January 2014); and

- EBSCO CINAHL (1982 to 7 January 2014).

We used the following search strategy in the Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor Pressure Ulcer explode all trees
#2 pressure NEXT (ulcer* or sore*):ti,ab,kw
#3 decubitus NEXT (ulcer* or sore*):ti,ab,kw
#4 (bed NEXT sore*) or bedsore:ti,ab,kw
#5 chronic NEXT ulcer*: ti,ab,kw
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Phototherapy explode all trees
#8 MeSH descriptor Laser Therapy explode all trees
#9 (phototherap* or "photoradiation therapy" or "photon therapy" or
"light therapy"):ti,ab,kw
#10 pulse* NEAR/3 light:ti,ab,kw
#11 pulse NEAR/3 (monochromic or monochromatic):ti,ab,kw
#12 light NEAR/3 monochromatic:ti,ab,kw
#13 wavelength NEAR/3 light:ti,ab,kw
#14 polarized NEAR/3 light:ti,ab,kw
#15 non-polarized NEAR/3 light:ti,ab,kw
#16 ("laser therapy" or LLLT or LPLT or LILT or (cold NEXT laser*) or
(therapeutic NEXT laser*) or (light NEXT emitting NEXT diode*) or LED or
(low NEXT reactive NEXT level NEXT laser*) or (diode NEXT laser*)):ti,ab,kw
#17 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18 (#6 AND #17)
We adapted this strategy to search Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL and these can be found in Appendix 1, Appendix 2 and Appendix 3 respectively. The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) (Lefebvre 2011). The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2011). There were no restrictions on the basis of date or language of publication.
We also searched the following ongoing trials databases using keywords including phototherapy and pressure ulcers

- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/index.html)
- ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)

Searching other resources

We searched the bibliographies of all articles retrieved for reports of any potentially relevant trials. We contacted the authors of included studies and asked for unpublished trial reports. One author (CC) contacted the suppliers of two phototherapy devices (Glorious Union Medtech Corp and Sure Care Products Co Ltd) to request information about additional studies. The relevant device information and intervention regimes were described clearly and confirmed via manufacturers' websites and handbooks.

Data collection and analysis

Selection of studies

Two review authors assessed the titles and abstracts identified for study relevance and design, according to the selection criteria. We obtained full-text articles of any reports that potentially satisfied the inclusion criteria. Two review authors checked these full papers for eligibility. Any disagreement was resolved by consensus and, if necessary, by referral to a third review author.

Data extraction and management

We extracted and summarised details of studies using a standardised data extraction sheet. We contacted the trial authors to request missing information for those studies that had been reported with data missing. We also contacted manufacturers of phototherapy devices to obtain additional information. When studies had been published more than once, we extracted data from all the reports, and nominated one as the primary reference. Two review authors extracted data independently. We extracted the following data:

- author; title; source of reference;
- country and publication year of study;
- setting of study (e.g. primary care);
- number and description of participants;
- intervention and comparison;
- co-interventions;
- treatment regimen (wavelength, duration, frequency, energy etc.);
- who delivered the treatment;
- outcomes and method of measurement;
- duration of follow-up;
- evaluation of cost, adverse events, pain data, quality of life data, length of hospital stay.

Assessment of risk of bias in included studies

Two review authors independently assessed each included study using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2011). This tool addressed specific domains, namely random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias (e.g. extreme baseline imbalance) (see Appendix 4 for details of criteria on which the judgments were based). Blinding and completeness of

outcome data for each outcome were assessed separately. We completed a 'Risk of bias' table for each eligible study. Any disagreement between the two review authors was discussed to achieve a consensus.

The assessments of risk of bias were presented in summary figure to illustrate all of the judgments in a cross-tabulation of studies. This display of internal validity indicates the weight the reader may give to the results of each study. Discrepancies were resolved through discussion with all review authors. We also appraised the quality of evidence by using the GRADE approach in relation to study limitations, inconsistency of results, indirectness, imprecision and risk of bias, as specified in the Handbook (Higgins 2011) and presented in the Summary of findings table.

Measures of treatment effect

We analysed data using RevMan 5.2 (RevMan 2011). We used risk ratio (RR) with 95% confidence interval (CI) as the effect measure for dichotomous outcomes. For continuous outcomes, we used the mean difference (MD), or, when the scale of measurement used differed across trials, the standardised mean difference (SMD [Hedge's*g*]). For time-to-event outcomes (e.g. time to healing), we used the hazard ratio (HR) with 95% CI.

Unit of analysis issues

Participants in the control and intervention groups were the primary unit of analysis. We did not include studies that analysed per ulcer because of the potential interaction between ulcers in a patient.

Dealing with missing data

We contacted trial authors for missing data. Sensitivity analyses were performed to assess how sensitive results are to reasonable changes in the assumptions that are made. For those trials with incomplete outcome data we followed the guidance in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Assessment of heterogeneity

We assessed clinical studies qualitatively, and assessed design heterogeneity on the basis of the participant, intervention, control, outcome and design elements listed in the 'Characteristics of included studies' table. We assessed statistical heterogeneity using the I^2 statistic (Higgins 2003).

Data synthesis

We synthesised data using Cochrane RevMan 5.2 software (RevMan 2011). Data synthesis depended on the quality, design and heterogeneity of the included trials. A meta-analysis was not performed if the clinical characteristics, methodology, or outcome measures were too diverse. All results were presented with 95% CIs. If data were inappropriate for pooling or analysis, for example, when there was high heterogeneity between interventions (types and regimes), or variation between populations or in stages of wounds, the results were presented narratively with discussion and agreed by reviewers.

Subgroup analysis and investigation of heterogeneity

If the included studies investigated similar populations and used similar variable and outcome definitions etc., we applied the fixed-effect model for meta-analysis. When the studies had high heterogeneity, we used the random-effects model for analysis, and explored the possible reasons behind the heterogeneity by performing further subgroup analysis. We performed subgroup analyses, when appropriate, to assess the impact of the grade of ulcer, study quality, type of intervention, participants and setting on the outcome, although we recognised that this would only be possible for trials that recruited and allocated participants on the basis of the grade of the ulcer.

RESULTS

Description of studies

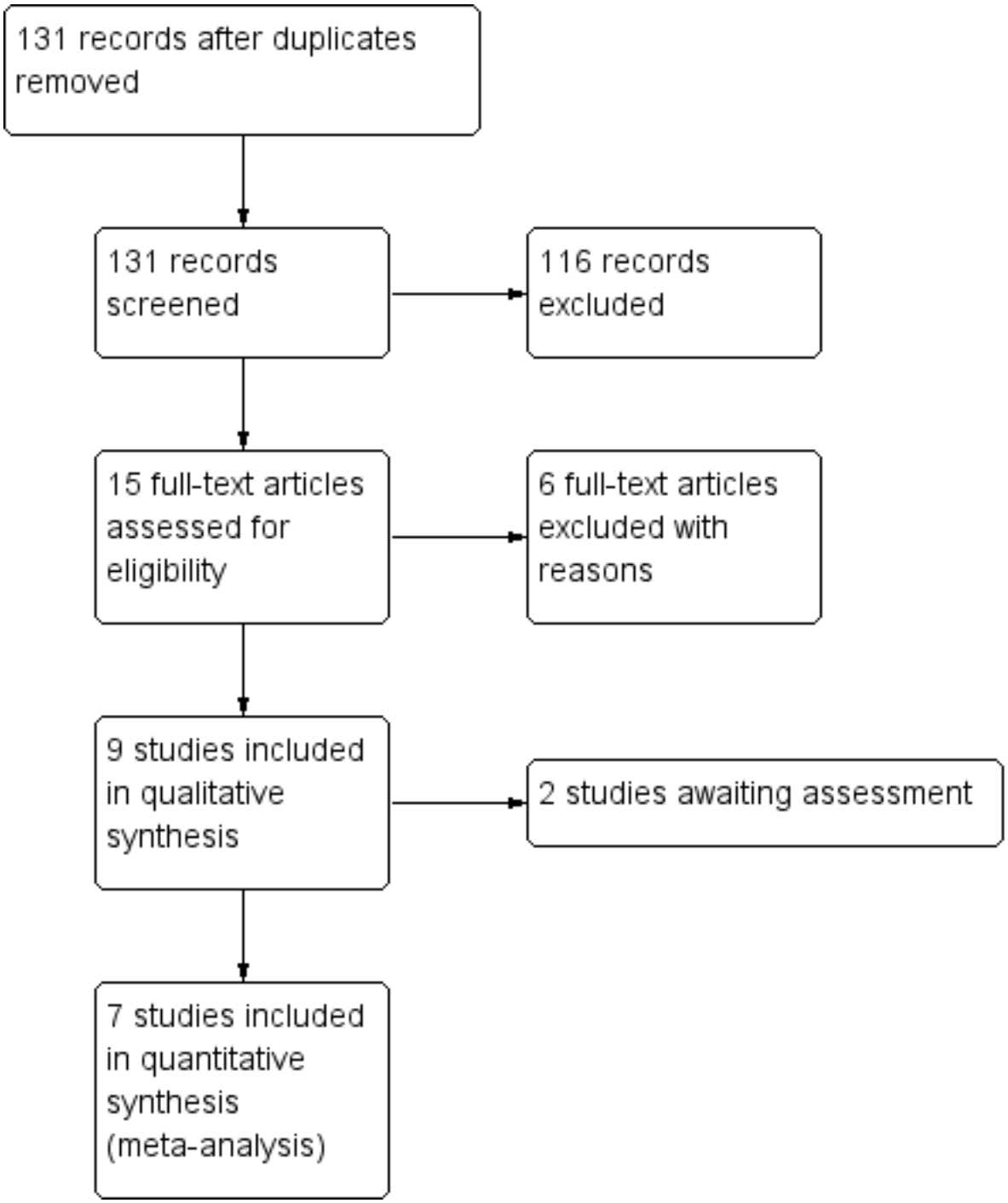
Results of the search

See: Characteristics of included studies; and Characteristics of excluded studies.

The initial search identified 131 titles after we had removed duplicates. Independent review of the abstracts by two review authors (CC, HWH) identified 15 articles that potentially met the inclusion criteria, or contained useful references, and we retrieved full text articles of these. Two review authors independently assessed the papers according to the inclusion and exclusion criteria.

There was complete agreement between the review authors, and seven papers, involving a total of 403 people, were included (Dehlin 2003; Durović 2008; Lucas 2003; Nussbaum 1994; Schubert 2001; Shojaei 2008; Wills 1983) (see Characteristics of included studies). The Characteristics of excluded studies table summarises details of the six studies that did not meet the inclusion criteria and were subsequently excluded from the review (Dolan 1989; Iordanou 2002; Mol 1994; Nussbaum 2013; Onigbinde 2010; Taly 2004). We are currently waiting for responses from the authors of two studies (Dehlin 2007; Lucas 2000), to clarify some information, and so these studies are currently classified as studies awaiting classification (Figure 1).

Figure 1. Study flow diagram.



Included studies

A summary of characteristics of the included studies is presented in the table of Characteristics of included studies. Seven studies are included in this review; one three-arm study (Nussbaum 1994), and six two-arm studies (Dehlin 2003; Durovic 2008; Lucas 2003; Schubert 2001; Shojaei 2008; Wills 1983). These studies were set in hospitals, nursing homes and outpatient settings. Trial sizes ranged from 16 to 198 participants. The seven studies were conducted from 1983 to 2008, included six different interventions (UVC, US, LLLT, Pulsed monochromatic light, polarized light therapy, diode laser). Four studies were conducted from Europe, two from North America and one from Asia.

Excluded studies

We excluded six studies. Two studies were not RCTs (Mol 1994; Onigbinde 2010). Two studies had applied the intervention and conventional treatments to individual participants, and ulcers were the unit of randomisation, and we were concerned that it might be difficult to separate any systemic effects when both treatments were applied to the same person (Iordanou 2002; Taly 2004). One study was excluded because the outcomes were reported for ulcers rather than participants, which violated our study protocol (Nussbaum 2013). Dolan 1989 had problems with randomisation and participants did not necessarily receive the intervention to which they had been allocated. See: Characteristics of excluded studies.

Risk of bias in included studies

The risk of bias in the included studies is summarised in Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

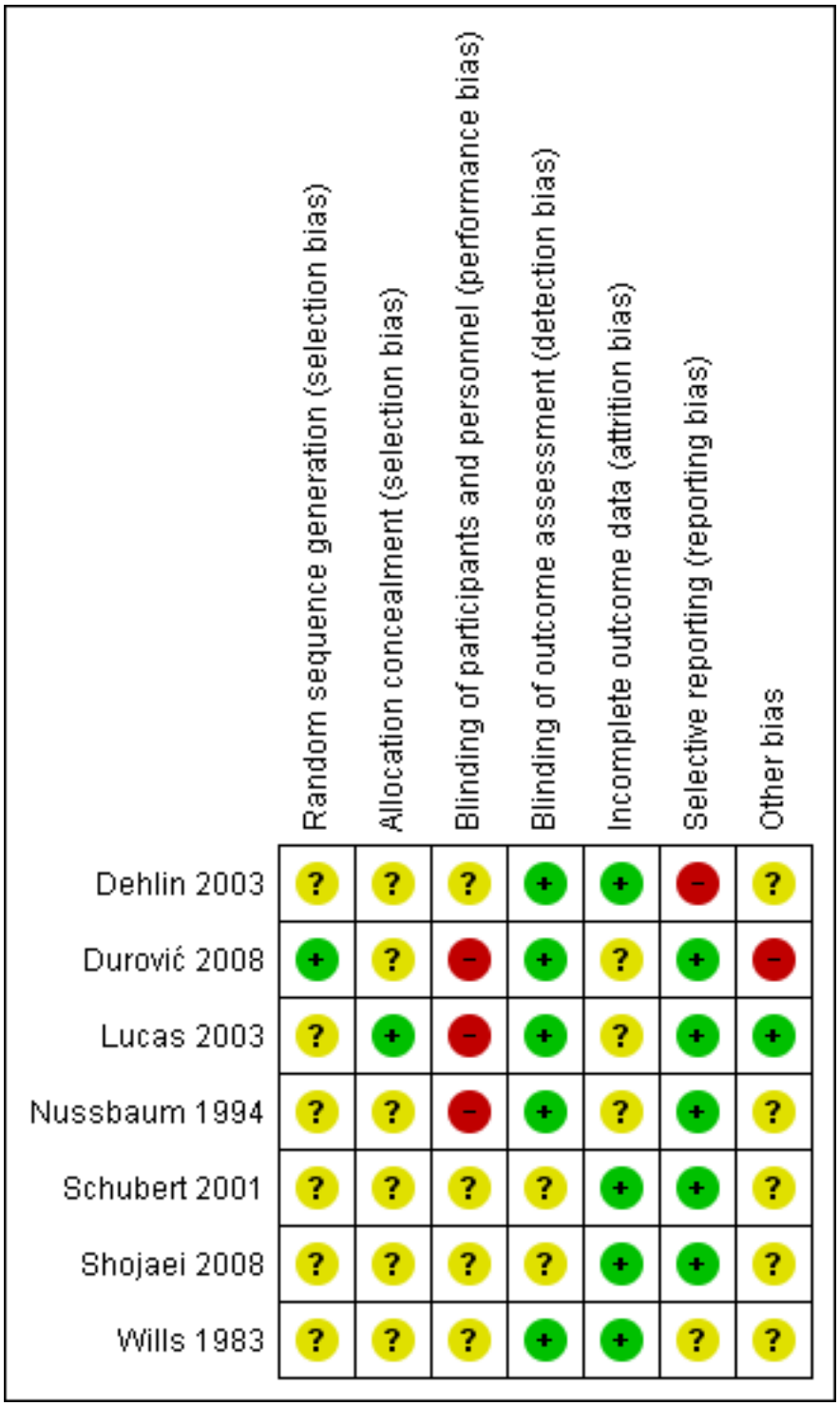
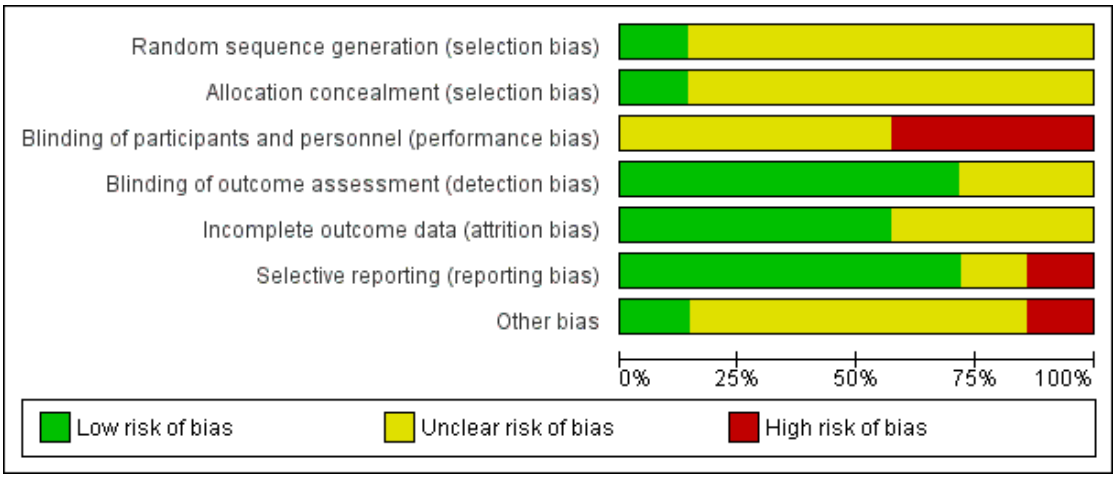


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Allocation

Generation of the randomisation sequence

Although all included studies stated that the participants were randomly allocated, only Durović 2008 reported the method used to generate the random sequence. Lucas 2003 used a centralised computerised telephone service, which could be considered to be a computer-generated sequence.

Allocation concealment

Most studies did not provide information about allocation concealment. They described the allocation to treatment groups as 'randomised' but provided no further description about how randomisation was achieved. Only Lucas 2003 mentioned that a central computerised telephone service was used for allocation, which could be considered to be low risk of selection bias .

Blinding

Blinding participants

One study provided a sham intervention as the control treatment (Dehlin 2003). In Wills 1983, mica was provided to cover the wound and provide blinding. However, blinding of participants might be difficult when the intervention is visually, or physically, obvious.

Blinding the person delivering the intervention

Outcomes may be influenced when trial-related personnel are aware of the group to which participants have been randomised. No study provided details about how they avoided performance bias.

Blinding the outcome assessors

All but two studies stated that outcome assessors were blinded (Schubert 2001; Shojaei 2008).

Incomplete outcome data

One study conducted intention-to-treat analysis, as there were no reported withdrawals (Shojaei 2008). Dehlin 2003 reported per-protocol analysis; 34 of the original 198 participants dropped out, mainly due to protocol violation, and were not included in the final analysis. Durović 2008 reported per-protocol analysis; eight of the original 48 patients dropped out for different reasons. Lucas 2003 reported analysis based on intention-to-treat; six out of the original 86 participants dropped out and no further explanation was provided. In Nussbaum 1994, four of the original 20 patients

did not complete the study due to medical complications or transfer to surgical treatment. In Schubert 2001, 13 out of the original 72 patients did not complete the study. Wills 1983 lost two of the 18 participants recruited: one participant died and another was transferred to an acute care hospital; neither was included in the data analysis. In general, except Dehlin 2003 study with unclear loss follow up reporting, the loss of follow up in both groups were balanced.

Selective reporting

Most studies presented data for outcomes listed in the methods sections of trial reports. In Dehlin 2003, however, outcomes mentioned in the methods section, such as almost complete healing (<10% remaining ulcer area) and time to partial healing (<50% remaining ulcer area) were not reported comprehensively. In Wills 1983, there was not sufficient information provided to permit a judgment to be made about selective reporting bias.

Other potential sources of bias

Data about baseline comparability for prognostic factors were worse in the control group in Durović 2008, which may have tended to favour the treatment effect.

Overall, the included studies were judged as being at unclear risk of bias and the majority of studies were unblinded.

Effects of interventions

See: **Summary of findings for the main comparison** Phototherapy versus control for treating pressure ulcers

Primary outcome measure

Time to complete healing

Two studies reported time to complete healing (Nussbaum 1994; Wills 1983), and a third the proportion of ulcers healed within specified time periods (Schubert 2001). In the Wills 1983 study, mean time to complete healing was 6.3 weeks in the UV treated group, significantly less than the mean of 8.4 weeks in the placebo group (P value < 0.02). Nussbaum 1994 provided information about time to complete healing (in weeks) in figures presented in the trial report. These data were on a per wound basis, with two participants having two ulcers. We defined the time to complete healing for these two participants as being the time by which both ulcers had completely healed. With results calculated individually in this manner, the time to complete healing was 4.6 weeks (n = 5 participants, SD 1.14) for the group that received ultrasound (US) and UV treatment; 12.6 weeks (n = 5 participants, SD 5.50) for the laser group; and 6.83 weeks (n = 6 participants, SD 3.19) for the control group (standard care). Data combined from these two studies showed the UV-treated group had a shorter mean time to complete healing than the control group (Nussbaum 1994; Wills 1983), with a mean difference of 2.13 weeks (95% CI -3.53 to -0.72) (P value 0.003; I^2 0%) (Analysis 1.1). Data for the Nussbaum 1994 laser group were not pooled in this analysis due to use of a different wavelength; however, the laser group exhibited a non-significant increase in the time to complete healing when compared with the control group (mean difference 5.77 weeks; 95% CI -0.25 to 11.79). The comparative risk was shown as the Summary of findings for the main comparison. This result should be interpreted with caution as this is a small study and the finding may be due to chance. We also note that to analyse time to complete healing data using mean and standard deviation (SD) is a compromise due, in this case, to the absence of appropriate data in the original studies. We recognise that the exclusion of censored participants (participants for whom the outcome is unknown, or whose ulcer did not heal) is very likely to introduce bias. Schubert 2001 reported the percentage of ulcers that had not reached a certain level of ulcer healing at each weekly measurement by using the Kaplan-Meier method of survival analysis. The group receiving phototherapy achieved 90% healing in five weeks, compared with nine weeks for the control group.

Proportions/number of ulcers healed

Three studies reported the proportion of ulcers healed (Dehlin 2003; Durović 2008; Shojaei 2008). Dehlin 2003 reported the number of ulcers healed at 12 weeks as 43.6% (34/78) in the phototherapy group and 39.5% (34/86) in the placebo group; the healing risk ratio (RR) was 1.10 (95% CI 0.77 to 1.59). Durović 2008 reported complete wound healing at four weeks of 10% (2/20) for the phototherapy group and 50% (10/20) for the placebo group; the healing RR in favour of placebo was 0.20 (95% CI 0.05 to 0.80). We did not pool the results of these two studies (Dehlin 2003; Durović 2008), because of the different treatment durations (Analysis 1.2). Shojaei 2008 reported that the difference in cure rate (minimum 50% reduction of ulcer size and improvement of at least one ulcer stage) between the two groups was statistically significant (P value 0.001) and in favour of the phototherapy group. There was a great deal of uncertainty surrounding these results, as the studies were small and all had an unclear risk of bias.

Adverse events/effects

Adverse effects were reported in two studies (Dehlin 2003; Lucas 2003). Dehlin 2003 reported 141 adverse events (participants n = 78) in the phototherapy group and 174 adverse events (participants n = 86) in the placebo group (RR 0.89, 95% CI: 0.71 to 1.12). Most of the adverse events were reported as unrelated to the treatment. Fve cases were considered related or possibly related to treatment, and these included tingling, pain, bleeding and redness. Lucas 2003, reported that 11% (5/44) of the participants

in the control group and 8% (3/37) of the participants in the LLLT group developed a stage 4 decubitus ulcer during the six-week study period (Fisher's exact test: P value 0.72). The risk ratio for adverse events was imprecise (RR 0.72, 95%CI 0.18 to 2.80)(Analysis 1.3).

Secondary outcomes

Rate of healing in ulcer area

Five studies reported on rate of ulcer healing (Dehlin 2003; Lucas 2003; Nussbaum 1994; Schubert 2001; Shojaei 2008). Dehlin 2003 reported no difference in the rate of change in ulcer area between the two groups (P value 0.18). Lucas 2003 reported absolute (mm^2) and relative (%) wound size reduction (over six weeks) which was analysed with Mann-Whitney U tests; there were no differences between the groups in either absolute improvement (P value 0.23) or relative improvement (P value 0.42) . Nussbaum 1994 reported the mean percentage change per week in ulcer size; 32.4% in the control group (six wounds), 53.5% in the US/UVC group (six wounds), and 23.7% in the laser group (six wounds). Schubert 2001 reported the rate of change in ulcer area (normalised ulcer area versus time); the healing rate was 39% greater in the phototherapy group compared to the control group. Shojaei 2008 reported downsizing of ulcers using the Wilcoxon test, and that there was no significant difference between groups (P value 0.236). Five studies reported the rate of change in ulcer area, three reported no difference between the groups. Whilst Schubert 2001 and Nussbaum 1994 reported improved healing for the phototherapy groups incomplete reporting of variance data means we are not able to verify these reports

Quality of life

Quality of life was not reported in any of the included trials.

Length of hospital stay

Length of hospital stay was not reported in any of the included trials.

Pain

Pain was not reported in any of the included trials.

Cost

Cost of treatment was not reported in any of the included trials.

DISCUSSION

Summary of main results

Overall, there was insufficient evidence to determine the relative effects of phototherapy for healing pressure ulcers. All studies had small sample sizes, which may have resulted in underpowered studies. Increasing the study size, which can increase precision and reduce the impact of unusual responses, may change study results.

Overall completeness and applicability of evidence

Important secondary outcomes such as quality of life, length of hospital stay, pain, and costs were not reported in the included studies. Some of the studies included are old, which limits the generalisability of our findings, as phototherapy has developed significantly over recent years. The mainstream therapy of pressure ulcers is still conventional wound care. The included studies did not provide enough evidence to support the use phototherapy in targeted pressure ulcer patients. Future studies should have a longer follow-up period to enable the long term effectiveness of phototherapy to be assessed thoroughly, and should also include information about the costs of the different treatments.

Quality of the evidence

Overall the evidence was very low quality. Some methodological issues required consideration and limited the strength of the conclusions that could be drawn from this review. The studies were small and underpowered, the mean sample size was 58 (range 16 to 164) which resulted in wide confidence intervals. The interventions used in the studies were diverse and applied in various participant groups and different stages of pressure ulcers as shown in the Summary of findings for the main comparison. Blinding was poorly reported, with incomplete blinding of investigators, participants, outcome assessors, and the data analyst, in most trials. Lack of blinding can introduce bias, particularly when outcomes are subjective, and may lead to potential over-estimation of the effect of the intervention, resulting in bias in favour of the treatment (Day 2000). However, blinding of participants and caregivers is difficult to achieve in wound care; blinding of outcome assessors is possible, and was achieved in only one trial (Shojaei 2008). Dehlin 2003 attempted to blind patients by using sham phototherapy, and Wills 1983 applied mica to the ulcer area; it is unclear how successful these methods were. Of the remaining four studies, three studies were at high risk of performance bias and unclear risk of detection bias (Durović 2008; Lucas 2003; Nussbaum 1994). One study had unclear risk of performance bias and low risk of detection bias (Schubert 2001). This resulted in

uncertainty about their risk of bias, as phototherapy and conventional therapy are different in both appearance and delivery.

Potential biases in the review process

There may be a risk of publication bias, as studies of phototherapy are frequently sponsored by the manufacturers of phototherapy devices. Results related to their products may not be published.

Agreements and disagreements with other studies or reviews

This review agrees with other related research with no evidence about the effect of phototherapy on wound healing (Hawkins 2007; Posten 2005; Sobanko 2008; Whinfield 2009). However, we found no other review that evaluated the specific therapeutic effects of phototherapy on pressure ulcers.

AUTHORS' CONCLUSIONS

Implications for practice

We are very uncertain as to the effects of phototherapy in the treatment of pressure ulcers. The small number of trials available for analysis, methodological limitations and small numbers of trial participants, meant that the possibility of benefits, or adverse effects, of this treatment cannot be ruled out. Overall, there was very low quality evidence about the effects of different approaches of phototherapy on treating pressure ulcers.

Implications for research

Trials comparing phototherapy with sham therapy, or standard care, are required to establish whether or not phototherapy improves the healing of pressure ulcers. In addition, future trials should explore whether particular sub-groups of participants are more likely than others to benefit from treatment with phototherapy, and, if the treatment is shown to be effective, to establish the point during the treatment regimen at which it should be applied. There is a need for further research in this area. It remains important that future studies be of sound methodological quality, and should incorporate the following.

- True randomisation.
- Adequate allocation concealment.
- Blinded outcome assessment.
- Use of objective outcome measurement (e.g. ulcer area, complete healing rates).
- Intention-to-treat analysis.
- Baseline comparability of groups (e.g. stratification for ulcer size or stage).
- Adequate sample sizes that ensure sufficient statistical power to detect true treatment effects.
- Reporting the results of the trial according to the CONSORT 2010 statement (Schulz 2010).

It is also recommended that studies should describe clearly the frequency and duration of treatment, location of wounds and any treatment applied concurrently with phototherapy.

Recruiting sufficient participants to participate in pressure ulcer studies can be difficult as many people with pressure ulcers appear to be incapacitated. Furthermore, when planning a trial in the pressure ulcer population, the death rate amongst participants during the study period is a major challenge. Ensuring sufficient participants are followed up to complete healing will always be difficult, and robust follow-up procedures need to take place. Potential solutions may involve exclusion of participants who are likely to die in the short-term, and use of survival analysis methods, which can use data from the participants up to the point of censoring (death). Nine of the 403 participants in the final analysis of these studies died during the trial period. If those withdrawn were taken into account after randomisation, seven out of 57 patients died. In modern inpatient settings, the movement of participants between wards and early discharge may pose alternative care risks compromising data collection. Given the considerable mortality rates in such short period of time in participants with pressure ulcers, healing may not be the most important outcome of interest. However, whether the patients will die or not may not be easy to predict at recruitment, and therefore in clinical practice the intervention would have to show benefit (both clinical and economic), even with such high death rates, as it is unlikely these patients would be denied treatment. More consideration should be given in future trials to quality of life and cost-effectiveness of the interventions, as these are important outcomes. There is a need to distinguish between the populations of participants with sacral, ischial and heel pressure ulcers, as the risk factors for healing in these differ, as well as the effects on a patient's quality of life.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dehlin 2003

Methods	RCT
Participants	164 (57 M; 107 F) participants in 8 geriatric centres with a grade II (87 participants) or grade III (77 participants) pressure ulcer. Ulcers were located on the trunk (74) and foot (90). Ulcer staging was defined by Shea Score (Shea 1975). Mobility status included "bedridden or wheelchair-bound" (104) and "walking with support" (59). The study was conducted in Sweden and Denmark
Interventions	Phototherapy group (n = 78): pulsed monochromatic light (Biolight® International AB, Sweden) A probe containing IR light at 956 nm and red light at 637 nm was pulsed at the following frequencies with a duty cycle of 80%: infrared light: 287 Hz, 31.2 Hz, 9900 Hz, 8 Hz, 15.6 Hz and 780 Hz; Red light: 8 Hz, 31.2 Hz, 9900 Hz, 5 Hz and 8.6 Hz IR at 55 W/m^2 was given first, and then red light at 21 W/m^2 Placebo group: (n = 86) white light diode painted red Both groups (placebo or phototherapy) were administrated according to fixed scheme: 5 days during week 1; 2 days during weeks 2, 3, 6, 8 and 10; and 3 days during week 3, 5, 7, 9 and 11. No phototherapy was administered on Saturdays or Sundays. Treatment duration was 9 min for the first 5 sessions (week 1) and 6 min for all remaining sessions Local wound treatment: all participants received the same conventional treatment, i. e. protection of the ulcer area, a regular turning schedule, emollient or moisturising cream around the ulcer, a pressure-reducing mattress, and a pressure-reducing cushion for wheelchair-bound participants. Hydrocellular/hydrocolloid bandages (Comfeel, Coloplast, Thigaderm) were applied to clean ulcers. Chemical or enzymatic debridement was not allowed
Outcomes	**PRIMARY OUTCOMES:** a) Number of ulcers healed at 12 weeks: b) Rate of change in ulcer area c) Time to complete healing (weeks) **SECONDARY OUTCOME:** d) Adverse effects:
Notes	This study was supported by Biolight Internal AB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: although the authors described this is a double-blind, randomised, placebo-controlled study, the process of randomisation was not clear and only mentioned in passing, "2 (patients)

Dehlin 2003 (*Continued*)

		because their pressure ulcer healed after screening but before randomisation" (p 260)
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the process of allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: interventions in 2 groups described as "The equipment for phototherapy and placebo was identical in appearance and both emitted red light. Intervention emitted both red light and infrared light. Placebo only emitted red light. No heating was seen from either treatment", which means that blinding of participants was possible (p 261). The blinding of personnel was not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: the authors stated, "the ulcer area of patients in all centres was determined by an independent individual using a planimeter . . . " (p 261)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: reasons for missing outcome data unlikely to be related to true outcome. 34 (17%) dropped out mainly due to protocol violation, a wish to withdraw, or because they experienced adverse events
Selective reporting (reporting bias)	High risk	Comment: the study protocol mentioned that grade II or III pressure ulcers were included, however, only the results of the grade II ulcers were reported in Figure 1
Other bias	Unclear risk	Comment: Exclusion criteria for this study lack of sufficient rationale and is likely to introduce other bias (p 260)

Đurović 2008

Methods	RCT
Participants	Recruited 48 participants with several kinds and locations of pressure ulcers. 4 participants refused to take part in the study, 2 participants were withdrawn from the phototherapy group and 2 participants in the control group died in second and third weeks of treatment Ulcers were located on the low part of back (1), right-low part of back (1), right buttock (1), left buttock (2), both buttocks (2), sacral area (15), right sacral-buttock area (1), right iliac spine (1), left hip (6), right hip (1), right heel (5), left heel (4) Inclusion criteria: people with a stage I-III ulcer according the Pressure Ulcer Classification System. No report on participants' mobility status This study was conducted in Serbia
Interventions	Phototherapy group (n = 20): polarised light therapy (Bioptron lamp) plus standard cleaning and dressing. A linear polarised light was used at wavelength: 400-2000 nm; degree of polarisation: > 95%; power density: 40 mW/cm^2; light energy: 2.4 J/cm^2, for 6

	min daily, at a distance of 10 cm, 5 times a week. Before the polarised light therapy, each wound was splashed with oxygen spray. All therapies were performed between 14:00 h and 16:00 h. Treatment lasted 4 weeks. All wounds were cleaned using 2% hydrogen peroxide Control group (n = 20): standard cleaning and dressing only, i.e. gauze with normal saline (NaCl), then a dry gauze, next to it a cotton wool and adhesive strip
Outcomes	**PRIMARY OUTCOME:** a) Completely healing of wound at 4 weeks **SECONDARY OUTCOMES**: b) Amount of exudate c) Wound surface
Notes	Information about study funding was not provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: probably done. The paper mentioned "the random divide was performed by the random number table" (p 907)
Allocation concealment (selection bias)	Unclear risk	Comment: no details provided about the strategy used to conceal allocation of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: this was a single blind study. The nature of the intervention under investigation makes blinding of participants and clinical professionals difficult
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment:described in methods section as "wound healing process was evaluated in a standard manner by two independent blinded observers" (p 908)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 2 participants withdrawn from both experimental and control groups. The reasons differed across groups: the two from the control group died, which may have been related to having a pressure ulcer. The later analysis is per-protocol rather than intention-to-treat
Selective reporting (reporting bias)	Low risk	Comment: all study outcomes have been reported
Other bias	High risk	Comment: participants significantly worse in the control group for 2 important baseline outcome measurements (surface and total PUSH score of pressure ulcer), which may have affected the treatment effect. Small sample size (n = 40) may have been a potential source of bias

Lucas 2003

Methods	RCT
Participants	Recruited 86 (32 M; 54 F) participants with a stage III pressure ulcer, from 3 nursing homes. Ulcers were located on the sacrum/coccyx (28), calcaneus (27), gluteal (12) , lateral malleolus (8), greater trochanter (1), medial femoral condyle (1), and other locations (9) Decubitus ulcer stage III was defined as a full-thickness skin defect extending into the subcutaneous layers and adipose tissue (NPUAP 1989). No report on participants' mobility status This study was conducted in Netherlands
Interventions	Phototherapy group (n = 39): LLLT treatments administered using a 12 microprocessor-controlled infrared Ga-AS-diode laser probe at 904 nm, covering an irradiated area of 12 cm^2 (physical probe dimension 30 cm^2). Total peak power was 12x70 W in a 830 Hz pulse frequency mode of 150 ns pulses with an average beam power of 12x8 mW and a radiant exposure of 1 J/cm^2, which required an exposure time of 125 s. The laser probe was applied to the surrounding normal tissue surface as a contact treatment, so that the centre of the applicator was held just off contact with the wound surface area (distance $\leq$ 1 mm). The beams, with a 2.5° angle of divergence, were applied perpendicularly to the tissue to achieve maximal penetration. Equal beam power was guaranteed by using lasers from 1 production process, which were calibrated in one machine(Combilaser C-501, Schreuder Medical, Amersfoort, the Netherlands) Control group (n = 47): conventional therapy All participants received the prevailing consensus decubitus ulcer treatment, as developed and recommended by NPUAP
Outcomes	**PRIMARY OUTCOME:** a) Absolute (mm^2) and relative (%) wound size reduction at 6 weeks compared to baseline **SECONDARY OUTCOMES:** b) the number of participants developing a stage IV ulcer c) the median change in Norton scores d) Adverse effects
Notes	Information about funding of this study was not provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: the study states "all patients were randomly assigned to one of the two treatment protocols: the control group or the experimental group" (p 73)
Allocation concealment (selection bias)	Low risk	Comment: the authors stated "allocation was by means of a central computerized telephone service."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: the authors did not provide information about how the participants and caregivers were blinded during the trial; there was no sham procedure for the control group, which meant

Lucas 2003 (*Continued*)

		that blinding was at high risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: authors stated "We performed a prospective, observer-blinded multicentre randomised clinical trail to assess the effect of . . .", also other information showed in methods session as "an investigator, not involved in the treatment, checked the output of the diode lasers every 2 months . . ." (p 73)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: primary outcome wound size and secondary outcome Norton score: 1/47 (2.12%) missing from control group 1/39 (2.56%) missing from intervention group. Missing outcome data balanced in numbers across 2 groups with similar reasons Secondary outcome stage IV ulcer: 3/47 (6.38%) missing from control group; 2/39 (5.12%) missing from intervention group. Missing outcome data balanced in numbers across 2 groups with similar reasons Although the authors mentioned that analysis was based on the intention-to-treat principle, the result provided was a per-protocol analysis for each group
Selective reporting (reporting bias)	Low risk	Comment: all study outcomes have been reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Nussbaum 1994

Methods	RCT
Participants	Hospitalised patients at Lyndhurst Spinal Cord Centre with a diagnosis of SCI and skin wounds. Participants' ulcers were located on the coccyx (5), ankle (4), trochanter (3) , chest (2), ischium (1), calf (1), heel (1), and thigh (1). Ulcer stages not defined. No report on participants' mobility status 20 participants (22 wounds) were randomly assigned to 3 groups This study was conducted in Canada
Interventions	US/UVC group (n = 5): pulsed US applied at a frequency of 3 MHz and a spatial average-temporal average intensity of 0.2 W/cm^2 (1:4 pulse ratio) for 5 minutes per 5 cm^2 of wound area. The UVC dosage (95% emission at 250 nm) was calculated for each session according to wound appearance. The dosage level was E_1 for clean/granulating areas, E_3 for purulent/slow-granulating areas, E_4 for heavily infected areas, and $2E_4$ for wound debridement Laser group (n = 6): Treatment was applied three times weekly using a cluster probe with an 820 nm laser diode and 30 superluminous diodes (10 at 660 nm, 880 nm, and 950 nm), and energy density of 4 J/cm^2, and a pulse repetition rate of 5000 pulses/s Wounds were traced every 14 days, and surface areas were calculated using the Sigma-Scan Measurement System Control group (n = 9): received standard wound care, consisting of wound cleansing

Nussbaum 1994 (*Continued*)

	twice daily using Hygeol (1:20), Jelonet dressings to keep the wound surface moist, and avoidance of lying or sitting positions that would cause pressure on existing ulcers A total of 16 participants (18 wounds) in both groups received standard wound care consisting of wound cleaning twice daily, application of moist dressings, and continuous relief of pressure until the wounds were healed
Outcomes	**PRIMARY OUTCOME:** a) time to complete healing **SECONDARY OUTCOMES:** b) mean percentage changes per week in ulcer size c) Adverse effects: no adverse effects reported
Notes	The study was funded by the John Labatt Seed Fund Award

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: the study only mentioned "patients who gave informed consent were randomly assigned . . . " p 814
Allocation concealment (selection bias)	Unclear risk	Comment: not addressed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: the authors did not provide information about how the patient and caregivers were blinded during the trial; there was no sham procedure in the control group, which meant that blinding was at high risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: the paper states "one investigator (ELN) was blinded to the subjects' group assignment" (p 816) and "All tracings were made by one investigator (ELN) who was not employed at the spinal cord centre and was blind to the subjects' group assignments. At the end of the study, the same investigator analysed the tracings using a digitiser tablet and stylus pen."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 4 participants (4/20, 20%) did not complete the study
Selective reporting (reporting bias)	Low risk	Comment: all study outcomes have been reported
Other bias	Unclear risk	Comment: small sample size (only 16 were analysed, although 20 recruited) and analysis based on wound rather than patient which may have been a potential source of bias

Schubert 2001

Methods	RCT
Participants	72 (26 M; 46 F) participants at the Huddings University Hospital in Sweden with stage II or III pressure ulcer. Most participants had falling trauma, which in 82% resulted in a fracture or an operation prior to the investigation. 54 participants had pressure ulcers located on the trunk. Ulcer staging was defined by Shea Score (Shea 1975). No mobility status was reported This study was conducted in Sweden
Interventions	Phototherapy group (n = 35): pulsed monochromatic light (Biolight® International AB, Sweden) A probe contained both 30 diodes, which emit IR light at 956 nm, and 80 diodes, which emit red light at 637 nm. First, it applied IR light with an irradiance of 55 W/m ^{2} (light dose rate measured with a Photo Research SpectraScanA Model PR-714), then red light with an irradiance of 21 W/m^2 (light dose rate measured with a SpectraScanA Colorimeter Model PR-650). Using a duty cycle of 80%, both the IR light and the red light were pulsed with the following pulse frequencies: for the first 5 treatments: 78 Hz, 702 Hz, 8.58 kHz; and for following treatments: 15.6 Hz, 287 Hz, 31.2 Hz. The probe was held approximately 3 cm above the ulcer, and was advanced around the ulcer surface to ensure even illumination of the whole area. Treatments were given for 9 min each time by 2 trained nurses. The number of treatments/week were: 5 in week 1; 4 in week 2; 2 in week 3; 1 in week 4 and beyond Placebo group (n = 37): conventional therapy only Both groups were given the same preventive information and local ulcer therapy prescribed by the investigator Local wound treatment: all participants received the same conventional treatment: protection of the ulcer area, a regular turning schedule, emollient or moisturising cream around the ulcer, a pressure-reducing mattress, and a pressure-reducing cushion for wheelchair-bound participants. Hydrocellular/hydrocolloid bandages (Comfeel, Coloplast, Thigaderm) were applied to clean ulcers. Chemical or enzymatic debridement was not allowed
Outcomes	**PRIMARY OUTCOMES:** a) Rate of change in ulcer area (normalised ulcer area versus time) b) Healing rate per week **SECONDARY OUTCOME:** c) Survival curves calculated with the Kaplan-Meier method to evaluate along with the ulcer healing progress
Notes	Financial support for this study was provided by Karolinska Institutet, Gun and Bertil Stohne's Foundation, and Biolight^{TM} International AB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: the study only mentioned "Randomisation was carried out in random permuted blocks of six patients prepared in advance" (p 33)

Schubert 2001 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: probably not done since no further details provided about whether the randomising schedule or assigning envelopes had appropriate safeguards
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: authors did not provided information regarding blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: the study did not report whether outcome assessor knew to which group participants belonged
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1 participant interrupted the study in week 5. 3 patients died during the course of the study, and 1 patient was not accessible for measurements for the last 2 weeks in control group. In phototherapy, 1 patient was further excluded after week 2 due to reoperation. Six patients died during the course of the study, and one patient was not accessible for measurements for the last 2 weeks
Selective reporting (reporting bias)	Low risk	Comment: all study outcomes have been reported
Other bias	Unclear risk	Insufficient information provided to assess whether an important bias exists

Shojaei 2008

Methods	RCT
Participants	Recruited 16 SCI veterans in Tehran with stage I (9 participants), II (4 participants) and III (3 participants) pressure ulcers in the following locations: ischial (10), sacral (4), and ankle (2). No report on participants' mobility status This study was conducted in Iran
Interventions	Phototherapy group (n = 8): supportive treatment and laser treatment using a GA-AL-AS laser and GA-AL-IN-PH diode laser (Azor-2k, Russia). Applied with contact using a continuous emission mode with probes: IR: 980 nm, 200 mW continuous (GA-AL-AS); and red light: 650 nm, 30 mW continuous (GA-AL-IN-PH). A dose of 4-6 J/cm^2 was applied every other day for 3 weeks Control group (n = 8): supportive treatment only
Outcomes	**PRIMARY OUTCOMES:** a) Reducing the size of ('downsizing') the ulcers b) Ulcer stage before and after treatment **SECONDARY OUTCOMES:** c) Ulcer size difference: comparing the ulcer size before and after treatment in both groups d) Reducing the size of ulcer: comparing the effect of treatment in reducing the size of

	ulcer in both groups e) Stage downgrade; f) The minimum 50% reduction in ulcer size; g) The difference of cure rate.
Notes	Source of funding for the trial was not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: the study only mentioned "they were selected in a convenient method and were randomly divided into case and control groups" (p 45)
Allocation concealment (selection bias)	Unclear risk	Comment: probably not done, since no further details are provided about whether the randomising schedule or assigning envelopes had appropriate safeguards
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: trial authors stated "The experimental study was designed as a randomised clinical trial with control and intervention groups in a triple blind setting" (p 45). However, the authors did not provided details of how the participants and caregivers were blinded during the trial; the absence of a sham procedure in the control group means that there is an unclear risk of bias for blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: trial authors stated " The data were filled into a form and were analysed by a statistician in a blind setting . . . " (p 45) However, the wound assessment process was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing outcome data in current study
Selective reporting (reporting bias)	Low risk	Comment: all study outcomes have been reported
Other bias	Unclear risk	Groups were not comparative at baseline with regard to stage of pressure ulcers. There were fewer stage 1 pressure ulcers in the control group (37.5%) than in the phototherapy group (75%) (p 46) The small sample size (n = 16) may have been a potential source of bias

Wills 1983

Methods	RCT
Participants	16 (6 M; 10 F) elderly participants residing in the Extended Care Unit of the Health Sciences Centre Hospital at the University of British Columbia and suffering from superficial pressure sores of recent onset of < 5 mm. 13 participants (81%) had ulcers located on ischium or sacrum. Ulcer stages were not defined. No report on participants' mobility status This study was conducted in Canada
Interventions	Phototherapy group (n = 8): conventional treatment and UV light treatment 2 times a week with doses 2.5 minimal erythemal dosage (comparable to second degree erythema) . The full course was 10 weeks. The UV source was a Kromayer lamp, i.e. a water-cooled mercury vapour lamp suitable for local irradiation (200-400 nm) that can be used in direct contact with the skin Control group (n = 8): conventional treatment only
Outcomes	**PRIMARY OUTCOME:** a) Time to complete healing **SECONDARY OUTCOME:** b) Adverse effects
Notes	This study was supported by a grant from the Canadian Geriatrics Research Society

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: the study only mentioned "patients were randomly allocated to a treatment group . . ." (p131)
Allocation concealment (selection bias)	Unclear risk	Comment: no further details regarding allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: the authors did not provide details about how the participants and caregivers were blinded during the trial: there was no sham procedure in the control group which makes the trial high risk for blinding. Although the authors described " . . . both patients and hospital staff were blind as to individual allocation" and the intervention in the control group was "the UV light was completely obstructed by a mica cap left in place over the quartz window" (p131-2) which could blind the patients , however, might not blind very well for staff
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: report states "No staff member was aware of the treatment category to which each patient belonged . . . " (p 132)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quotation: "One died and one was transferred to an acute care hospital" (p 132)

Wills 1983 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information provided to make a judgment
Other bias	Unclear risk	Comment: small sample size (n = 18) may have been a potential source of bias

Abbreviations
< = less than
≤ = less than or equal to
F = female
GA-AS = gallium-arsenide
GA-AL-AS = gallium-aluminium-arsenide
GA-AL-IN-PH = gallium-aluminium-indium-phosphate
h = hour(s)
IR = infrared
LLLT = low-level laser therapy
M = male
min = minute(s)
NPUAP = (American) National Pressure Ulcer Advisory Panel
PUSH = Pressure Ulcer Scale for Healing
RCT = randomised controlled trial
s = second(s)
SCI = spinal cord injury
UV = ultraviolet
UVC = ultraviolet C
US = ultrasound

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Dolan 1989	The report for this trial was written in Dutch. In this study, participants were selected randomly and divided into groups using a list (not specified further). However, participants did not receive the treatment allocated because of ethical problems. Initially, 4 groups were randomly selected and had to be classified as a list. However, those participants with smaller wounds for whom favourable progress was expected, were then reassigned to the placebo and control groups. Therefore, the number of participants in control and placebo groups were much smaller compared to the intervention groups. The poor quality of the data reported led to difficulties with interpretation of data
Iordanou 2002	This study examined the effect of polarised light on pressure ulcers in participants with 2 pressure ulcers. The process by which each ulcer was assigned to a group is not clear. Since phototherapy may have a systemic effect, it may be difficult to separate out the true effect between the 2 groups. This study was excluded because, according to our review protocol, the required unit for inclusion in the review is participants, not ulcers

(*Continued*)

Mol 1994	The report for this study was written in Dutch. This study was not randomised or quasi-randomised. The authors state that an independent co-worker allocated participants to the intervention and control groups, ensuring equal wound surface and male:female ratio in both groups
Nussbaum 2013	This study examined the effect of UVC irradiation on pressure ulcers in participants with 1 or more pressure ulcers. We excluded the study because reporting of outcomes was based on ulcers instead of participants. In our protocol, the required unit for inclusion in the review is participants, not ulcers
Onigbinde 2010	The study design was a non-randomised matched cohort design
Taly 2004	This study examined the effect of multi-wavelength light therapy on pressure ulcers in participants who might have had more than one ulcer. The process of randomisation was based on ulcers rather than participants, which contravenes our requirements for inclusion in the review. Furthermore, since phototherapy may have a systemic effect, it could be difficult to separate out the true effect of phototherapy treatment

Characteristics of studies awaiting assessment *[ordered by study ID]*

Dehlin 2007

Methods	Paper that presents a combined analysis from 2 trials that were conducted at different time periods (see Notes)
Participants	163 (62 M; 101 F) participants in 8 geriatric centres with a grade II pressure ulcer. Ulcers were located on the trunk (92) or foot (71). Ulcer staging defined by Shea Score. Mobility status included "bedridden or wheelchair-bound" (88) and "walking with support" (62). The study was conducted in Sweden and Denmark 87 of the participants in the analysis were from a previous study (Dehlin 2003), and the remainder from the more recent study (Dehlin 2007).
Interventions	Phototherapy group (n = 78): pulsed monochromatic light (Biolight® International AB, Sweden) using a probe containing IR light at 956 nm and red light at 637 nm pulsing at the following frequencies: IR: 287 Hz, 31.2 Hz, 9900 Hz, 8 Hz, 156 Hz red light: 8 Hz, 31.2 Hz, 9900 Hz, 5 Hz and 8.6 Hz. IR 55 W/m^2 given first, then red light 21W/m^2 Placebo group (n = 86): white light diode painted red Intervention for both groups was administrated according to fixed schedule: 5 days for week 1; 2 days for weeks 2, 3, 6, 8 and 10; 3 days for weeks 3, 5, 7, 9 and 11. No phototherapy was administered on Saturdays or Sundays. Treatment duration was 9 min for the first 5 sessions (week 1) and 6 min for all remaining sessions Local wound treatment: all participants received the same conventional treatment: protection of the ulcer area, a regular turning schedule, emollient or moisturising cream around the ulcer, a pressure-reducing mattress, and a pressure-reducing cushion for wheelchair-bound participants. Hydrocellular/hydrocolloid bandages (Comfeel, Coloplast, Thigaderm) were applied to clean ulcers. Chemical or enzymatic debridement was not allowed
Outcomes	**PRIMARY OUTCOME:** a) Rate of change in ulcer area (the mean normalised reduction in pressure ulcer size) **SECONDARY OUTCOMES:** b) Number of ulcers healed at 12 weeks c) Time to complete healing (days) d) Adverse effects

Dehlin 2007 (*Continued*)

Notes	This study presents the combined analysis of results from 87 participants with grade II ulcers from a previous study, Dehlin 2003, with 76 participants from a trial conducted several years later. We have written to the author requesting the data for the 76 participants randomised in the subsequent study so that these data can be presented separately in the meta-analysis

Lucas 2000

Methods	RCT
Participants	Consecutive patients with stage III pressure ulcers were eligible from 4 nursing homes. This study was conducted in Netherlands
Interventions	All patients received the prevailing consensus decubitus ulcer treatment; whereas one group(n=8) had LLLT in addition. LLLT treatments were administered using an LLLT device with a microprocessor controlled optical source probe.The control group (n=8) was provided with the standard treatment only
Outcomes	**PRIMARY OUTCOME**: No treatment-related adverse effects were reported during this study **SECONDARY OUTCOME**: the median wound area (mm2) at six weeks after the intervention startedChange of wound surface area
Notes	We checked the study period and settings between Lucas 2000 and Lucas 2003 and found that study subjects and data in Lucas 2000 was unclear and may overlapping with the Lucas 2003. We moved Lucas 2000 to the section of studies awaiting classification.

Abbreviations
F = female
M = male
RCT = randomised controlled trial
min = minute(s)

DATA AND ANALYSES

Comparison 1. Phototherapy versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to complete healing (weeks)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Ultra violet vs control	2	24	Mean Difference (IV, Random, 95% CI)	-2.13 [-3.53, -0.72]
1.2 Laser vs control	1	8	Mean Difference (IV, Random, 95% CI)	5.77 [-0.25, 11.79]
2 Proportions/number of ulcers healed	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

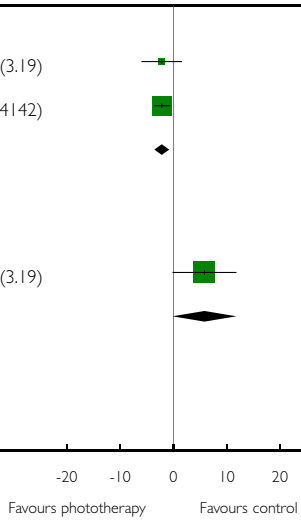
Analysis 1.1. Comparison 1 Phototherapy versus control, Outcome 1 Time to complete healing (weeks).

Review: Phototherapy for treating pressure ulcers

Comparison: 1 Phototherapy versus control

Outcome: 1 Time to complete healing (weeks)

Study or subgroup	Phototherapy N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Ultra violet vs control							
Nussbaum 1994	5	4.6 (1.14)	3	6.83 (3.19)		14.1 %	-2.23 [-5.98, 1.52]
Wills 1983	8	6.26 (1.6688)	8	8.37 (1.4142)		85.9 %	-2.11 [-3.63, -0.59]
Subtotal (95% CI)	**13**		**11**			**100.0 %**	**-2.13 [-3.53, -0.72]**
Heterogeneity: Tau² = 0.0; Chi² = 0.00, df = 1 (P = 0.95); I² =0.0%							
Test for overall effect: Z = 2.97 (P = 0.0030)							
2 Laser vs control							
Nussbaum 1994	5	12.6 (5.5)	3	6.83 (3.19)		100.0 %	5.77 [-0.25, 11.79]
Subtotal (95% CI)	**5**		**3**			**100.0 %**	**5.77 [-0.25, 11.79]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.88 (P = 0.060)							
Test for subgroup differences: Chi² = 6.26, df = 1 (P = 0.01), I² =84%							

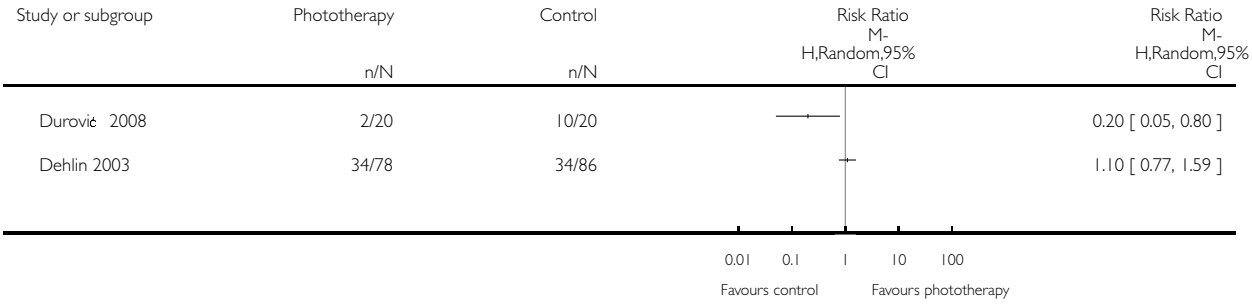


Analysis 1.2. Comparison 1 Phototherapy versus control, Outcome 2 Proportions/number of ulcers healed.

Review: Phototherapy for treating pressure ulcers

Comparison: 1 Phototherapy versus control

Outcome: 2 Proportions/number of ulcers healed

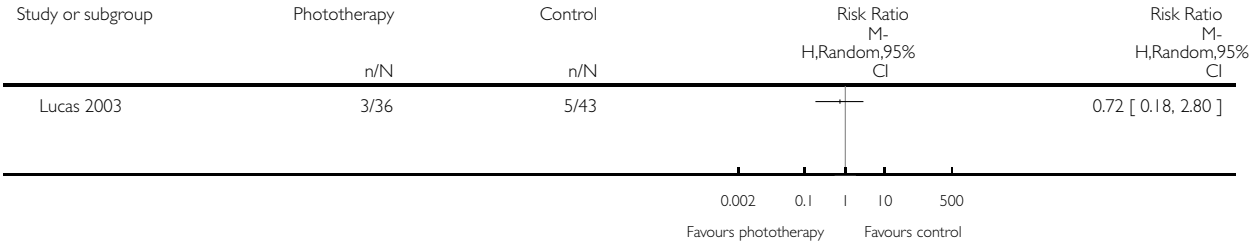


Analysis 1.3. Comparison 1 Phototherapy versus control, Outcome 3 Adverse events.

Review: Phototherapy for treating pressure ulcers

Comparison: 1 Phototherapy versus control

Outcome: 3 Adverse events



APPENDICES

Appendix 1. Ovid MEDLINE search strategy

1 exp Pressure Ulcer/
2 (pressure adj (ulcer* or sore*)).tw.
3 (decubitus adj (ulcer* or sore*)).tw.
4 (bedsore* or bed sore*).tw.
5 chronic ulcer*.tw.
6 or/1-5
7 exp Phototherapy/
8 exp Laser Therapy/
9 (phototherap* or photoradiation therapy or photon therapy or light therapy).tw.
10 (pulse* adj3 light).tw. (974)
11 (pulse* adj3 (monochromic or monochromatic)).tw.
12 (light adj3 monochromatic).tw.
13 (wavelength adj3 light).tw.
14 (polarized adj3 light).tw.
15 (non-polarized adj3 light).tw.
16 (laser therapy or LLLT or LPLT or LILT or cold laser* or therapeutic laser* or light emitting diode* or LED or low reactive level laser* or diode laser*).tw.
17 or/7-16
18 6 and 17
19 randomized controlled trial.pt.
20 controlled clinical trial.pt.
21 randomized.ab.
22 placebo.ab.
23 clinical trials as topic.sh.
24 randomly.ab.
25 trial.ti.
26 or/19-25
27 (animals not (humans and animals)).sh.
28 26 not 27
29 18 and 28

Appendix 2. Ovid EMBASE search strategy

1 exp decubitus/ (9307)
2 (pressure adj (ulcer* or sore*)).tw. (5758)
3 (decubitus adj (ulcer* or sore*)).tw. (799)
4 (bedsore* or bed sore*).tw. (416)
5 chronic ulcer*.tw. (1463)
6 or/1-5 (11892)
7 exp phototherapy/ (39268)
8 exp Low Level Laser Therapy/ (9961)
9 (phototherap* or photoradiation therapy or photon therapy or light therapy).tw. (6263)
10 (pulse* adj3 light).tw. (2534)
11 (pulse adj3 (monochromic or monochromatic)).tw. (9)
12 (light adj3 monochromatic).tw. (515)
13 (wavelength adj3 light).tw. (1679)
14 (polarized adj3 light).tw. (2953)
15 (non-polarized adj3 light).tw. (14)

16 (laser therapy or LLLT or LPLT or LILT or cold laser* or therapeutic laser* or light emitting diode* or LED or low reactive level laser* or diode laser*).tw. (266174)
17 or/7-16 (308019)
18 6 and 17 (284)
19 Clinical trial/ (714455)
20 Randomized controlled trials/ (28044)
21 Random Allocation/ (50961)
22 Single-Blind Method/ (15709)
23 Double-Blind Method/ (86533)
24 Cross-Over Studies/ (32153)
25 Placebos/ (167510)
26 Randomi?ed controlled trial$.tw. (81537)
27 RCT.tw. (10784)
28 Random allocation.tw. (918)
29 Randomly allocated.tw. (14415)
30 Allocated randomly.tw. (1220)
31 (allocated adj2 random).tw. (265)
32 Single blind$.tw. (9760)
33 Double blind$.tw. (91286)
34 ((treble or triple) adj blind$).tw. (243)
35 Placebo$.tw. (138875)
36 Prospective Studies/ (203440)
37 or/19-36 (1068393)
38 Case study/ (16343)
39 Case report.tw. (168936)
40 Abstract report/ or letter/ (515163)
41 or/38-40 (696119)
42 37 not 41 (1039474)
43 animal/ (727596)
44 human/ (8724562)
45 43 not 44 (486704)
46 42 not 45 (1017156)
47 18 and 46 (57)
48 (2012* or 2013*).em. (1576450)
49 47 and 48 (4)

Appendix 3. EBSCO CINAHL search strategy

S31S18 and S30
S30S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29
S29MH “Quantitative Studies”
S28TI placebo* or AB placebo*
S27MH “Placebos”
S26TI random* allocat* or AB random* allocat*
S25MH “Random Assignment”
S24TI randomi?ed control* trial* or AB randomi?ed control* trial*
S23AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S22TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S21TI clinic* N1 trial* or AB clinic* N1 trial*
S20PT Clinical trial
S19MH “Clinical Trials+”
S18S6 and S17

S17S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16
S16TI ("laser therapy" or LLLT or LPLT or LILT or cold laser* or therapeutic laser* or light emitting diode* or LED or low reactive level laser* or diode laser*) or AB ("laser therapy" or LLLT or LPLT or LILT or cold laser* or therapeutic laser* or light emitting diode* or LED or low reactive level laser* or diode laser*)
S15TI non-polarized N3 light or AB non-polarized N3 light
S14TI polarized N3 light or AB polarized N3 light
S13TI light N3 wavelength or AB light N3 wavelength
S12TI light N3 monochromatic or AB light N3 monochromatic
S11TI (pulse* N3 monochromic or pulse* N3 monochromatic) or AB (pulse* N3 monochromic or pulse* N3 monochromatic)
S10TI pulse* N3 light or AB pulse* N3 light
S9TI (phototherap* or "photoradiation therapy" or "photon therapy" or "light therapy") or AB (phototherap* or "photoradiation therapy" or "photon therapy" or "light therapy")
S8(MH "Laser Therapy+")
S7(MH "Phototherapy+")
S6S1 or S2 or S3 or S4 or S5
S5TI chronic ulcer* or AB chronic ulcer*
S4TI decubitus or AB decubitus
S3TI (bed sore* or bedsore*) or AB (bed sore* or bedsore*)
S2TI (pressure ulcer* or pressure sore*) or AB (pressure ulcer* or pressure sore*)
S1(MH "Pressure Ulcer")

Appendix 4. Risk of bias assessment

1. Was the allocation sequence randomly generated?

Low risk of bias

The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

High risk of bias

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

Unclear

Insufficient information provided about the sequence generation process to permit a judgement of low or high risk of bias.

2. Was the treatment allocation adequately concealed?

Low risk of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.

High risk of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially-numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

Insufficient information provided to permit a judgement of low or high risk of bias. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially-numbered, opaque and sealed.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias

Any one of the following.

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others was unlikely to introduce bias.

High risk of bias

Any one of the following.

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others was likely to introduce bias.

Unclear

Either of the following.

- Insufficient information provided to permit a judgement of low or high risk of bias.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following.

- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes was not enough to have a clinically relevant impact on observed effect size.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following.

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

Either of the following.

- Insufficient reporting of attrition/exclusions to permit a judgement of low or high risk of bias (e.g. number randomised not stated, no reasons for missing data provided).
- The study did not address this outcome.

5. Are reports of the study free of suggestion of selective outcome reporting?

Low risk of bias

Either of the following.

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias

Any one of the following.

- Not all of the study's pre-specified primary outcomes have been reported.
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified.
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear

Insufficient information provided to permit a judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias

Low risk of bias

The study appears to be free of other sources of bias.

High risk of bias

There is at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- had extreme baseline imbalance; or
- has been claimed to have been fraudulent; or
- had some other problem.

Unclear

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

Chiehfeng Chen: conceived, designed and co-ordinated the review. Extracted data, assessed quality, analysed and interpreted data. Performed statistical analysis and checked quality of statistical analysis. Wrote and edited the review. Secured funding and performed previous work that was the foundation of the current review. Wrote to study authors, experts and companies. Approved final review prior to submission and is a guarantor of the review.

Wen-Hsuan Hou: conceived, designed and co-ordinated the review. Extracted data, assessed quality, analysed and interpreted data. Performed statistical analysis. Completed the first draft of the review, advised on the review and approved final review prior to submission.

Edwin SY Chan: conceived and designed the review. Checked quality of data extraction and checked quality assessment. Checked quality of statistical analysis. Advised on and made an intellectual contribution to the review. Approved final review prior to submission.

Mei-Ling Yeh: conceived and designed the review. Extracted data and assessed quality, analysed and interpreted data. Performed statistical analysis. Advised on the review and approved final review prior to submission.

Heng-Lien Daniel Lo: co-ordinated the review. Extracted data and checked quality of data extraction. Analysed and interpreted data. Performed statistical analysis. Completed first draft of the review and contributed to writing and editing the review. Advised on the review and approved final review prior to submission.

Contributions of editorial base

Joan Webster: Approved the final review prior to submission.
Sally Bell-Syer: co-ordinated the editorial process. Advised on methodology, interpretation and content. Edited the review.
Rachel Richardson: edited the review.
Ruth Foxlee: designed the search strategy.
Amanda Briant: ran the searches and edited the search methods section for the review.

DECLARATIONS OF INTEREST

Chiehfeng Chen: nothing to declare

Wen-Hsuan Hou: nothing to declare

Edwin SY Chan: nothing to declare

Mei-Ling Yeh: nothing to declare

Heng-Lien Daniel Lo: nothing to declare

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not perform the subgroup analyses to test the effect of study quality, participants and setting on the outcome because of limited data reported in the included studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Phototherapy [*methods]; Pressure Ulcer [*therapy]; Randomized Controlled Trials as Topic; Time Factors; Ultraviolet Therapy [methods]; Wound Healing

MeSH check words

Humans