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DOI:
10.1002/14651858.CD013530

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Pressure-garment therapy for preventing hypertrophic scarring after burn injury.
Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD013530.
DOI: 10.1002/14651858.CD013530.

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[Intervention Protocol]

Pressure-garment therapy for preventing hypertrophic scarring after burn injury

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Editorial group: Cochrane Wounds Group
Publication status and date: New, published in Issue 1, 2020.

Citation: Harris IM, Lee KC, Deeks JJ, Moore DJ, Moiemen NS, Dretzke J. Pressure-garment therapy for preventing hypertrophic scarring after burn injury. *Cochrane Database of Systematic Reviews* 2020, Issue 1. Art. No.: CD013530. DOI: 10.1002/14651858.CD013530.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of pressure garment therapy for the prevention of hypertrophic scarring after burn injury.

BACKGROUND

Description of the condition

Burn damage to skin, caused by thermal, electrical or chemical sources, is a common injury worldwide (Peck 2011). In 2004, approximately 11 million people suffered a burn requiring medical attention globally (WHO 2008). It is estimated that there are over 300,000 deaths from burn injuries every year, with the vast majority (over 95%) occurring in low- and middle-income countries (WHO 2018). A recent systematic review found that the incidence and severity of burns occurring in high-income countries are on a downward trend attributed to advances in burn care, socioeconomic development, and burn prevention programmes, but evidence for low- and middle-income countries is lacking (Smolle 2017). Most burns are not fatal, but the resultant scarring can cause both cosmetic and functional problems (Ripper 2009). Whilst scar formation is an inevitable consequence of injury to the skin (Urioste 1999), in some individuals failure of normal wound-healing processes results in excessive scar tissue formation, termed 'hypertrophic scarring' (Atiyeh 2007). The exact mechanism resulting in hypertrophic scar formation is poorly understood, but there is some evidence to suggest that derailed immunological responses are responsible for an exaggerated inflammatory phase early in the wound-healing process (Van der Veer 2009). Estimates suggest that hypertrophic scarring affects 1.5% to 4.5% of the general population, with hypertrophic scarring following a burn injury affecting 32% to 67% of people with burns (Atiyeh 2007). Hypertrophic scarring is red, thick, and rigid, and causes a variety of problems including pain, itching, and reduced movement in affected areas (Bloemen 2009; Friedstat 2014). It tends to occur within four to eight weeks following injury (Gauglitz 2011). Keloid scarring may also occur after burn injury in genetically susceptible individuals but is relatively rare. Keloid scarring is similar in appearance to hypertrophic scarring, but keloid scarring spreads beyond the margins of the original wound whereas hypertrophic scarring does not. Keloid scarring can develop later than hypertrophic scarring, up to several years after the initial injury (Gauglitz 2011). Keloid scars are treated very differently to hypertrophic scars (Gauglitz 2013), and as such will not be the subject of this review.

Many factors are involved in the development of hypertrophic scarring, such as age, ethnic group, and hormone levels, as well as the burn size, thickness, and location (Niessen 1999). The involvement of these factors in hypertrophic scar formation is poorly understood, and robust evidence is currently lacking (Butzelaar 2016). However, it is generally accepted that the most important factor in predicting the development of hypertrophic scarring is healing time, which is related to burn size and thickness (Chipp 2017; Miller 2005).

There are many methods of assessing scars based on various factors such as colour, texture, and thickness. The most commonly used subjective assessment scales are the Patient and Observer Scar Assessment Scale (POSAS) and the Vancouver Scar Scale (VSS) (Bae 2014). Laser imaging, ultrasound imaging, cutometer, colorimetry, and 3D cameras can also be used for objective scar assessment (Lee 2016). Current recommendations are that a panel of devices should be used for comprehensive scar assessment (Lee 2016).

Description of the intervention

The most commonly used method for the prevention and treatment of hypertrophic scarring is pressure-garment therapy (PGT) (Anzarut 2009; Engrav 2010; Ward 1991), which costs the NHS approximately GBP 2.2 million a year (Moiemen 2018). PGT involves the wearing of tight elastic garments in the area of the burn as soon as wound healing has occurred and pressure therapy can be tolerated. The garments should be worn for 23 hours a day (allowing removal for up to one hour for bathing and personal care), for an average of 12 to 18 months, depending on scar severity (Anzarut 2009; Yildiz 2007). There are two main types of pressure garments: ready-to-wear/pre-sized garments and custom-made garments. Ready-to-wear garments have the advantages of being immediately available and cheaper than custom-made garments, but adjustments are usually required for a better fit and to ensure they exert enough pressure (Macintyre 2006). The exact amount of pressure required is not known (Atiyeh 2013; Huang 2013), but it is thought that less than 15 mmHg and more than 40 mmHg does not result in the required effect (Bloemen 2009; Park 2011). Most typically, pressures of 15 to 25 mmHg are used in clinical settings (Ai 2017; Sharp 2007). There is some evidence to indicate that pressures over 30 mmHg are harmful (Ai 2017). The exact amount of pressure exerted by a garment is often not known, particularly where the reduction method is used for manufacture. With this method the dimensions of the body part with the burn wound are measured and the garment is made with a 10% to 20% reduction factor for that measurement (Atiyeh 2013). Exerted pressure may also not be uniform and depends on factors such as curvature of the body part, and the underlying type of tissue; there is also a loss of tension over time (Atiyeh 2013).

Wearing pressure garments can be challenging for several reasons, including discomfort (itching, pain, sweating), embarrassment at wearing the visible garments, and the demands of the duration and intensity of treatment (Johnson 1994; Macintyre 2006; Ripper 2009). Such challenges can result in treatment dropout rates of 30% to 59% in adults (Ripper 2009). Factors shown to help improve patient adherence to PGT include good social support and a good doctor-patient relationship (DiMatteo 2004; Moiemen 2018; Ripper 2009).

Other forms of treatment, used independently of or in conjunction with PGT, include silicone sheets/sprays/gels applied to the burn, corticosteroid injections, and laser therapy (Bloemen 2009). These treatments are thought to variously influence wound collagen remodeling, inflammation or angiogenesis or both, but the exact mechanisms of action have not been fully elucidated (Atiyeh 2013). They are most likely to be used in combination with PGT rather than as an alternative.

How the intervention might work

PGT is thought to work in two ways, by affecting collagen remodelling during the wound-healing process. Firstly, the tight pressure restricts blood flow, and therefore oxygen availability, to the scar, which is thought to accelerate the maturation of the scar (Clark 1996; Ripper 2009). Secondly, the constant pressure exerted on the scar tissue forces the collagen fibres of the new tissue to grow systematically and more in line with the normal pattern of healthy skin fibres (Clark 1996; Ripper 2009). Pressure garment therapy is therefore most effective if initiated when the wound is fully closed but the scar is still fragile and likely to break down (Bloemen 2009).

For best results the pressure garments need to be worn until scar maturation.

Why it is important to do this review

Scarring can have serious functional and cosmetic implications, and may negatively impact upon patients' quality of life (Atiyeh 2013; Ripper 2009). Scarring is very visible due to the differences in colour, pigmentation, and texture of affected tissue and can lead to psychological problems such as stigmatisation and low self-esteem. Scarring can also be very uncomfortable in terms of pain, pruritus, and dryness (Ai 2017). Interventions aim to improve functionality in terms of both work and leisure activities (Atiyeh 2013).

PGT in its currently-used form originated in the 1970s from a leading burns centre in the USA where immediate improvement of hypertrophic scarring was observed in individuals with major burns (Atiyeh 2013). The practice spread widely to other centres in the USA and beyond, despite the lack of well-designed clinical trials to show the efficacy of PGT (Moiemen 2018). This was probably facilitated by the ready availability of the garments, and substantial industry involvement and drive towards commercialisation (Linares 1993). PGT is now standard care in almost all burn centres globally, but there is continued uncertainty around its effectiveness, including perceived benefit to its recipients (Moiemen 2018).

Laser treatment and percutaneous needling are gaining recognition as viable options to treat hypertrophic scarring, but these treatments are used only after scar maturation (Finnerty 2016).

A systematic review (Anzarut 2009) based on six studies was unable to draw definitive conclusions. A more recent systematic review (Ai 2017) included 12 studies and found some evidence of improvement as measured by the VSS score and in pigmentation, redness and scar hardness. Inclusion was limited to studies using a pressure of 15 to 25 mmHg. There appeared to be insufficient consideration of heterogeneity in the analyses, with studies being pooled regardless of comparator (no and low pressure), age (adults and children) or co-intervention (e.g. pressure therapy and silicone). It was also unclear if data included in meta-analyses were based on intention-to-treat analyses, and whether studies not included in the meta-analyses reported relevant outcomes. Adverse events and compliance were also insufficiently considered. Since the publication of this systematic review, there has been at least one other relevant study (Pegasus) (Moiemen 2018) and there are a number of ongoing studies.

A complete assessment of all the evidence, including full consideration of heterogeneity (including different levels of pressure), all comparator groups and all relevant outcomes is therefore warranted.

OBJECTIVES

To assess the effects of pressure garment therapy for the prevention of hypertrophic scarring after burn injury.

METHODS

Criteria for considering studies for this review

Types of studies

We will include published and unpublished randomised controlled trials (RCTs), including (i) between-patient comparisons where participants are either allocated to the intervention or to a comparator, and (ii) split-body designs, where different wounds within the same participant are allocated to different treatments. We will place no restriction by publication status or language. We will exclude studies using quasi-randomisation.

Types of participants

We will include RCTs recruiting people in any population or care setting and with any size, depth or cause of burn (thermal, electrical, or chemical) who are likely to develop hypertrophic scarring and who are suitable for hypertrophic scarring prevention therapy. People likely to develop hypertrophic scarring are those whose wounds have taken around three or more weeks to heal or who have received skin grafts as a result of their burn injury. We do not anticipate health equity issues within the eligible populations.

Types of interventions

We will include studies with PGT (any pressure) alone or in combination with other scar-management therapies. We will include any RCT in which the use of PGT (any type or duration of treatment), a difference in pressure or the type of pressure garment during the treatment period is the only systematic difference between treatment groups.

Types of comparison

Any other type of scar-management treatment not including PGT, or PGT using a different (lower) pressure, or a different type of pressure garment. We will not include studies comparing different durations of the same PGT.

Types of outcome measures

Primary outcomes

The extent of hypertrophic scarring assessed by scar-rating scales such as the Vancouver Scar Scale (VSS) and the Patient and Observer Scar Assessment Scale (POSAS) or other verified assessment scale with results reported as mean and standard deviation (SD), or median and range. Scar-rating scales attempt to quantify overall scar severity by measuring a range of scar parameters, such as thickness, vascularity, pigmentation and pliability. Some, such as the POSAS, also include pain and pruritus. There is currently no 'gold standard' scar-rating scale, as none are thought to include all aspects relevant to patient quality of life (e.g. cosmetic, functional or psychological aspects) (Nguyen 2015).

We will distinguish between outcome reporting in the short term (less than six months) and longer term (6 - 12 months; 12 - 18 months; > 18 months), as findings are unlikely to be comparable.

Secondary outcomes

- Individual scar parameters (surface area/volume, texture, thickness, vascularity, pigmentation and pliability), regardless of how measured (subjective, e.g. observer- or participant-rated,

or objective, or both, e.g. using a measurement tool such as a colorimeter or tonometer)
- Range of movement (ROM) assessment (where the scar is above a joint), measured using a goniometer
- Pain measured by any relevant scale/tool
- Pruritus measured by any relevant scale/tool
- Adverse events/complications (e.g. wound breakdown and blistering), where this is reported as the proportion of participants in each group with an adverse event
- Participant health-related quality of life/health status, measured using a standardised generic questionnaire such as EQ-5D, SF-36, SF-12 or SF-6, or wound-specific questionnaires such as the Burn Specific Health Scale–Brief (BSHS-B)
- Adherence to therapy
- Any other outcome measuring the impact of the burn/scar on the participant (e.g. the Brisbane Burn Scar Impact Profile)

Outcomes in paediatric trials may be parent-reported. Outcomes affecting the participant as a whole (such as quality of life) cannot be measured where a randomised controlled trial has a split-body design.

We note that at present there are no clinically-defined minimum important differences or thresholds for either the primary or secondary outcomes.

Search methods for identification of studies

Electronic searches

We will search the following databases to retrieve reports of relevant trials:

- the Cochrane Wounds Specialised Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (latest issue);
- Ovid MEDLINE (from 1946 onwards);
- Ovid Embase (from 1974 onwards);
- EBSCO Cumulative Index to Nursing and Allied Health Literature (CINAHL Plus); from 1937 onwards.

We have devised a draft search strategy for CENTRAL which is displayed in Appendix 1. We will adapt this strategy to search the Cochrane Wounds Specialised Register, Ovid MEDLINE, Ovid Embase and EBSCO CINAHL Plus. We will combine the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2019). We will combine the Embase search with the Ovid Embase filter terms developed by the UK Cochrane Centre (Lefebvre 2019). We will combine the CINAHL Plus search with the trial filter developed by Glanville 2019. There will be no restrictions of the searches by language, date of publication or study setting.

We will also search the following clinical trials registries for ongoing studies:

- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/trialsearch).

Searching other resources

We will search the bibliographies of all retrieved and relevant publications identified by these strategies for further studies. We will contact experts in the field to ask if they have been involved in or know of any studies relevant to this review. We will also contact JOBST®, Jobskin®, Gottfried Medical Inc. and DM Orthotics Ltd. to ask for information relevant to this review. We do not plan to carry out any handsearching.

Data collection and analysis

Selection of studies

Two review authors (IMH, KCL) will independently screen titles and abstracts, using the eligibility criteria described. They will both screen full texts where a decision cannot be made on the basis of title or abstract or both, resolving disagreements though discussion or through consulting a third review author (NM). We will use a PRISMA flow diagram for documenting the selection process and reasons for exclusion (Liberati 2009). We will use EndNote X7 to manage the screening process.

Data extraction and management

Two review authors (IMH, KCL) will independently extract data using a standardised and piloted data extraction form. We will resolve disagreements through discussion or through consulting a third review author (NM or JD). Key data to be extracted will include:

- study characteristics and methods: year of publication, study design, randomisation method and unit of randomisation, start date, country of study, setting, length of follow-up;
- participants: number, age, inclusion and exclusion criteria, percentage male, severity and cause of burn;
- intervention: type of garment, time from 95% healing to starting PGT, duration of treatment period, pressure used, any other therapies used;
- comparator therapy: standard care, other therapies, (lower) pressure used;
- primary and secondary outcomes: method of scar improvement assessment, how measured, time points measured, scores at baseline/post-treatment (intervention and control groups), change scores, summary scores;
- funding and potential conflicts of interest among the study authors.

We will record the data in Review Manager 5 (Review Manager 2014). We will contact authors for missing outcome data.

Assessment of risk of bias in included studies

Two review authors (IMH, KCL) will independently assess risks of bias of included randomised controlled trials, using the Cochrane 'Risk of bias' tool which is displayed in Appendix 2. Domains relate to selection bias, performance bias, detection bias, attrition bias and reporting bias and other potential forms of bias. Due to the nature of the intervention, it is difficult to blind participants or those administering the intervention. Blinding may be possible to an extent where different pressures are compared (e.g. high versus lower/ineffective pressure). As pressure garments are by design tight-fitting, they can leave marks on the skin when removed, so blind outcome assessment of scars may also be difficult to achieve. Review authors will make a decision of 'low', 'high' or 'unclear'

risk of bias based on the criteria given for making 'Risk of bias' judgements. We will assess risks of bias separately for different outcomes where there are differences in, for example, blinding and loss to follow-up. We will record reasons underpinning the decisions. The review authors will resolve disagreements though discussion or through consulting a third review author (JD).

Measures of treatment effect

Most outcomes are likely to be continuous, e.g. changes on scar-rating or quality-of-life scales, and we will use the mean difference with its 95% confidence interval (MD, 95% CI) for quantitative synthesis. When comparing the difference between groups, we will give preference to a follow-up score adjusted for baseline (using ANCOVA) compared with a change score. Where trials measure the same outcome using different scales, we will consider using the standardised mean difference (SMD, 95% CI) as a summary statistic in any meta-analysis of such data. We will use the risk ratio (RR, 95% CI) for dichotomous data (e.g. adverse event data). Where risk ratios are not reported it may be possible to calculate them from raw data. We do not anticipate any time-to-event data.

Unit of analysis issues

Studies may randomise participants, but may conduct analysis by wound/scar. If there is one wound/scar per participant, then the person will be the unit of analysis. Where randomised participants have several wounds, they need to be considered as participant 'clusters'. We will consider whether authors have used analysis methods to account for such clustering. Where trials include a mixture of participants with one or more wounds (individual and clustered data), then we will note this as a concern as part of the 'Risk of bias' assessment.

Studies may also measure within-participant differences, where two or more wounds are treated differently, or one half of a wound is treated differently from the other half. Additional 'Risk of bias' considerations are likely to arise from a within-participant design, e.g. relating to choice of site for each treatment or blinding of outcome evaluation across the same site. We will consider whether paired analysis has been undertaken to account for the within-participant design and will record this as part of the 'Risk of bias' assessment.

We will present all data, but we will only take appropriately-analysed data forward for meta-analysis. If studies use multiple intervention arms compared with a single control, we will split the control group to avoid unit-of-analysis errors. If more than one intervention is used in a treatment arm, we will analyse this as a single combined treatment (e.g. PGT with silicone).

Dealing with missing data

We will contact authors if relevant outcome data are insufficiently reported. We will also contact authors of ongoing trials and relevant conference abstracts for interim or additional data. Where measures of variance are missing we will calculate them if possible. For analyses, we will use data based on an intention-to-treat analysis where possible, e.g. based on last observation carried forward (LOCF) for continuous data. If studies have reported dichotomous outcomes (e.g. the proportions with and without a certain level of improvement) and there are missing data, we will assume for the purpose of analysis that the improvement was not achieved. We will test the impact of this assumption in a sensitivity analysis where we will assume that the improvement was achieved.

Assessment of heterogeneity

We will consider clinical and methodological heterogeneity before deciding whether to combine data quantitatively. Sources of clinical heterogeneity will relate to the type of therapy (e.g. level of pressure, additional scar-management techniques), comparator (e.g. alternative pressure, different therapy) and population (aged 16 or under versus adult). There may also be differences in length of follow-up and use of outcome measures, e.g. types of scar-assessment tool. Methodological heterogeneity will relate to the type of randomisation, e.g. between participants or within participant. We will base judgements about statistical heterogeneity on the Chi^2 test and I^2 statistic values (Deeks 2017).

Assessment of reporting biases

We will try to minimise reporting biases by searching multiple databases and clinical trial registries. As part of the 'Risk of bias' assessment we will look for incompletely-reported or missing outcome data. We will assess the possible presence of publication bias using funnel plots where at least 10 studies are included in a meta-analysis, and will visually inspect the plot for signs of asymmetry. We will not conduct statistical tests for asymmetry. We note that, based on scoping searches, there are unlikely to be more than 10 studies within an individual meta-analysis.

Data synthesis

We will group findings first by comparison (PGT versus standard care only; PGT versus lower pressure treatment; PGT versus an alternative intervention; different types of pressure garment) and then by outcome, and time point (< 6 months; 6 - 12 months; 12 - 18 months; > 18 months). We will undertake meta-analyses where we consider studies with the same comparator and reporting the same outcome (and outcome metric) to be reasonably similar in terms of clinical and methodological characteristics. As there is likely to be some heterogeneity between studies in terms of participant and intervention characteristics, we will use a random-effects model. A fixed-effect approach is unlikely to be appropriate, as the assumption that a single underlying treatment effect is being estimated is unlikely to be correct. We will not combine split-body and standard RCT studies in meta-analyses.

We will also measure statistical heterogeneity, but will not use it to decide on whether or not to undertake each meta-analysis. Where we do undertake meta-analyses, we will use the Chi^2 test to give an indication of whether there is statistically significant heterogeneity. As we expect relatively few studies to be in the individual meta-analyses (fewer than 10), we will set the significance level at $P < 0.1$. We will also use the I^2 statistic to quantify the amount of heterogeneity beyond that expected by chance, and will use guidance outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* to interpret I^2 (Deeks 2017).

We will use forest plots to present summary estimates (mean difference or risk ratio) with 95% confident intervals. Where the same outcome is measured using different scales, we will use the standardised mean difference (SMD, 95% CI) as a summary statistic. We will also consider the representation of subgroups in forest plots without overall pooling. Results from studies not included in meta-analyses will be summarised in tables.

Subgroup analysis and investigation of heterogeneity

We will explore whether it is possible to subgroup studies by age (e.g. infants, younger/older children, and adults) and by location of burn (e.g. limbs, trunk, head, face). Subgrouping by burn severity is unlikely to be possible, given that burns in a person may be a mixture of superficial and deep burns. We will present any results from subgroup analyses undertaken by the primary study authors where these align with our prespecified subgroups described above, i.e. age and location of burn.

As described in the Data synthesis section, we will group studies by length of follow-up time. It is thought that pressure garments should be used for at least six to 18 months, so outcomes between studies with short-term (less than six months) and longer-term follow-up (6 - 12 months; 12 - 18 months; > 18 months) are unlikely to be comparable. If studies report this, we will also look at whether there are any differences in time from 95% healing to start of PGT, as the starting point may affect outcome. We will explore the effect of including or excluding studies of different study design (within-participant or between-participant randomisation) where possible.

We will explore differences between subgroups using random-effects meta-regression.

Sensitivity analysis

We will use 'Risk of bias' assessment findings to guide interpretation of our findings. We will consider sensitivity analyses based on study quality, by removing any studies classified as being at overall ‘high’ risk of bias. However this will be contingent on the number of studies in a meta-analysis, the completeness of reporting of quality criteria and evidence of clear differences in the risk of bias between studies.

We will also explore the effect of excluding studies where intention-to-treat data are not available.

'Summary of findings' tables and GRADE assessment of the certainty of evidence

We will present the main results for the review in 'Summary of findings' tables, which will include a list of the important outcome measures, numbers of studies measuring the outcomes and numbers of participants, measures of effect (size and uncertainty) and overall certainty of evidence based on GRADE (Schünemann 2013). We will rate the certainty of the body of evidence as high, moderate, low, or very low, depending on the directness of the evidence in addressing the study question/s, the risks of bias in the included studies (methodological quality), the precision of effect estimates, the consistency of the evidence (degree of heterogeneity), and the risk of publication bias (Schünemann 2013). We will undertake this on an outcome-by-outcome basis. The absence of clinically-defined minimum important differences for primary or secondary outcomes means it will not be possible to use this information in making decisions on rating of imprecision. Where analysis of an outcome is not possible due to lack of data, we will present the reasons for this in the table.

We plan to include the following outcomes in the 'Summary of findings' tables:

- Scar improvement assessed by scar-rating scales such as the Vancouver Scar Scale (VSS) and the Patient and Observer Scar Assessment Scale (POSAS);
- Scar parameters such as thickness, vascularity, pigmentation and pliability;
- Pain;
- Pruritis;
- Adverse events/complications (wound breakdown and blistering);
- Quality of life;
- Adherence to therapy.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the contributions of peer reviewers Harun Juwale, Pinar Avsar, Duncan Chambers and Jacky Edwards. They would also like to thank Kate Cahill who copy edited the protocol.

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APPENDICES

Appendix 1. The Cochrane Central Register of Controlled Trials (CENTRAL) draft search strategy

#1 MeSH descriptor: [Burns] explode all trees

#2 (burn or burns or burned or scald* or postburn* or post-burn*):ti,ab,kw

#3 ((thermal or chemical or alkali or acid or electric*) next injur*):ti,ab,kw

#4 #1 or #2 or #3

#5 MeSH descriptor: [Cicatrix] explode all trees

#6 ((hypertroph*) near/3 (cicatri* or scar or scars or scarred or scarring)):ti,ab,kw

#7 #5 or #6

#8 #4 and #7

#9 MeSH descriptor: [Compression Bandages] explode all trees

#10 MeSH descriptor: [Pressure] explode all trees

#11 MeSH descriptor: [Clothing] explode all trees

#12 MeSH descriptor: [Occlusive Dressings] explode all trees

#13 ((pressure or compression or elastic or ace) near/3 (garment* or bandag* or stocking* or hosiery or wrap* or therap*)):ti,ab,kw

#14 (mmHg):ti,ab,kw

#15 (jobskin or jobst or tubigrip or tubi-grip or tubi grip or lymed or tricolast or urgosyval):ti,ab,kw

#16 (PGT):ti,ab,kw

#17 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 #8 and #17

Appendix 2. Risk of bias assessment tool for randomised controlled trials

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 about the sequence generation process provided 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: use of an open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. envelopes were unsealed, non-opaque, 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 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 likely to introduce bias.

Unclear

Either of the following:

- Insufficient information to permit 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 are unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data are 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 the observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, a plausible effect size (difference in means or standardised difference in means) among missing outcomes is not enough to have a clinically relevant impact on the 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 are likely to be related to the true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is enough to induce clinically relevant bias in the intervention effect estimate.
- For continuous outcome data, a plausible effect size (difference in means or standardised difference in means) among missing outcomes is enough to induce a clinically relevant bias in the observed effect size.
- 'As-treated' analysis done with a 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 prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).

High risk of bias

Any one of the following:

- Not all of the study's prespecified primary outcomes have been reported.
- One or more primary outcomes is/are reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified.
- One or more reported primary outcomes was/were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review is/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
- 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

Isobel Harris: developed the protocol; co-ordinated the protocol development; produced the first draft of the protocol; contributed to writing or editing the protocol; approved final version of the protocol prior to submission.

Kwang Chear Lee: developed the protocol; contributed to writing or editing the protocol; advised on the protocol; approved final version of the protocol prior to submission.

Jonathan Deeks: secured funding; contributed to writing or editing the protocol; advised on the protocol; approved final version of the protocol prior to submission.

David Moore: contributed to writing or editing the protocol; advised on the protocol; approved final version of the protocol prior to submission.

Naiem Moiemen: conceived the review question; secured funding; contributed to writing or editing the protocol; advised on the protocol; approved final version of the protocol prior to submission.

Janine Dretzke: developed the protocol; co-ordinated the protocol development; produced the first draft of the protocol; contributed to writing or editing the protocol; approved final version of the protocol prior to submission; is guarantor of the protocol.

Contributions of the Editorial Base

Jo Dumville (Joint Co-ordinating Editor): edited the protocol; advised on methodology, interpretation and content; approved the final version of the protocol prior to submission.

Gill Rizzello (Managing Editor): coordinated the editorial process; advised on content; edited the protocol.

Sophie Bishop (Information Specialist): designed the search strategy and edited the search methods section.

Tom Patterson (Editorial Assistant): edited the reference sections.

DECLARATIONS OF INTEREST

Isobel Harris: none known.

Kwang Chear Lee: none known.

Jonathan Deeks: is a co-investigator of the PEGASUS study, which will be eligible for inclusion in the review.

David Moore: none known.

Naiem Moiemen: is the chief investigator of the PEGASUS study, which will be eligible for inclusion in the review.

Janine Dretzke: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

  This project was supported by the NIHR via Cochrane Infrastructure funding to Cochrane Wounds. The views and opinions expressed are those of the authors and not necessarily those of the NIHR, NHS or the Department of Health and Social Care.