ClinicalEvidence

Vitiligo in adults and children: surgical interventions

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ABSTRACT

INTRODUCTION: Vitiligo is an acquired skin disorder characterised by white (depigmented) patches in the skin, due to the loss of functioning melanocytes. The extent and distribution of vitiligo often changes during the course of a person's lifetime and its progression is unpredictable. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of surgical interventions for vitiligo in adults and in children? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2014 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found four studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: blister grafts, cultured cellular transplantation, non-cultured cellular transplantation, punch/mini grafts, and split thickness skin grafts.

QUESTIONS

INTERVENTIONS

Key points

- Vitiligo is an acquired skin disorder characterised by white (depigmented) patches in the skin, caused by the loss of functioning melanocytes.

  Vitiligo patches can appear anywhere on the skin, but common sites are usually around the orifices, the genitals, or sun-exposed areas such as the face and hands.

  The extent and distribution of vitiligo often changes during the course of a person's lifetime, and its progression is unpredictable.

- Vitiligo patches in certain body areas such as the acral sites, palms and soles, lips, mucosa, and nipples, and segmental forms in any area are relatively resistant to all conventional medical treatment modalities. This is thought to be related to the lack of melanocyte reservoir in non-hair bearing sites.

  In these cases, counselling and cosmetic camouflage become a priority, and often in these sites re-pigmentation is unlikely to be achieved unless surgical methods are used.

- There are a variety of medical treatments used for vitiligo, but this review has focused on surgical therapeutic options as this is an expanding field worldwide. Surgery is considered in people with stable vitiligo unresponsive to standard medical therapies.

  We do not know whether surgical treatments of vitiligo in adults and children (blister grafts, cultured cellular transplantation, non-cultured cellular transplantation, punch/mini grafts, split-thickness skin grafts) are effective, as we found limited evidence from RCTs and systematic reviews. The evidence found was of low or very low quality.

  We searched for RCTs comparing blister grafts, cultured cellular transplantation, non-cultured cellular transplantation, punch/mini grafts, and split-thickness grafts with no active treatment or with each other.

  There are significant challenges undertaking robust RCTs assessing surgical treatments, as it is difficult to offer suitable control treatments and the high cost of surgical studies can be limiting.

Clinical context

GENERAL BACKGROUND

Vitiligo is an acquired skin disorder characterised by white (depigmented) patches in the skin, caused by the loss of functioning melanocytes. It is difficult to assess the true prevalence of vitiligo as the estimate of prevalence worldwide, between 0.5% and 1.0%, varies according to cultural and social differences. Figures as high as 9% have been reported in India where stigma associated with the disease is high.

FOCUS OF THE REVIEW

There are a variety of medical treatments used for vitiligo, but this review has focused on surgical therapeutic options as this is an expanding field worldwide. Surgery is considered in people with stable vitiligo unresponsive to standard medical therapies.

COMMENTS ON EVIDENCE

The evidence found was of low or very low quality. There are significant challenges undertaking robust RCTs assessing surgical treatments, as it is difficult to offer suitable control treatments and the high costs of surgical studies can be limiting .

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, March 2010, to April 2014. A search back-dated to 1966 was performed for the new options added to the scope at this update. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 30 studies. Appraisal of titles and abstracts led to the exclusion of 17 studies and the further review of 13 full publications. Of the 13 full articles evaluated, two systematic reviews and two RCTs were added at this update.

DEFINITION

Vitiligo is an acquired skin disorder characterised by white (depigmented) patches in the skin, caused by the loss of functioning melanocytes. The hair, and rarely the eyes, may also lose colour. Vitiligo patches can appear anywhere on the skin but common sites are usually around the orifices, the genitals, or sun-exposed areas such as the face and hands. The disease is classified according to its extent and distribution, and can be subdivided into generalised or localised. In practice, there is considerable overlap between these types, and people often have vitiligo that cannot be categorised or that will change during the course of their lifetime. Therefore, for the purposes of this review, we have included all people diagnosed with vitiligo of any type. Children were defined as people aged 15 years and under. In developing guidelines for the management of vitiligo, [1] a consensus was agreed among clinicians that topical corticosteroid therapy would be chosen as first-line treatment for localised vitiligo (11/14 respondents [79%]), generalised vitiligo (11/14 respondents [79%]), and stable vitiligo (12/14 respondents [86%]). Other treatments options include topical tacrolimus for localised vitiligo and narrowband ultraviolet light B (UVB) or oral psoralen plus ultraviolet light A (PUVA) for moderate to severe generalised vitiligo. Surgery is considered in people with stable vitiligo unresponsive to conservative medical therapies. Stable disease is generally defined as no new lesions, no change in existing lesions, absence of koebnerisation, and spontaneous re-pigmentation. The time period for this is undefined but can range from 6 months to 3 years. The approach taken by surgical therapies is to add melanocytes into the depigmented patches of skin, taken from other pigmented areas. Currently, two types of surgery are considered, tissue grafting or cellular grafting procedures. In this review we have included split-thickness skin grafts, blister grafts, and punch/mini-grafts, which are types of tissue grafting, and cultured and non-cultured cellular transplantation, as types of cellular grafting.

INCIDENCE/ PREVALENCE

Vitiligo is estimated to affect 1% of the world's population, regardless of age, sex, and skin colour. [2] [3] Anyone of any age can develop vitiligo, but it is very rarely reported present at birth. In a Dutch study, 50% of people reported that the disease appeared before the age of 20 years. [4] [5] It is difficult to assess the true prevalence of vitiligo as the estimate of prevalence worldwide varies between 0.5% and 1.0% according to cultural and social differences. In countries where more stigma is attached to the disease for cultural or social reasons, or because it is more visible due to dark skin colour, more people with the disease are likely to consult a doctor than in other countries where this is not the case, thus reported estimates of prevalence may be high. Figures as high as 9% have been reported in India where stigma associated with the disease is high. [6]

AETIOLOGY/ RISK FACTORS

The aetiology of vitiligo is uncertain, although genetic, immunological, biochemical (including oxidative stress), and neurogenic factors may interact to contribute to its development. [2] [7] [8] [9] Although there are few epidemiological studies of vitiligo, it is believed that one third of people with vitiligo report close family members affected by the disorder, [10] suggesting that genetic factors have an important role in the development of the disease. This is supported by several genetic susceptibility studies. [11] [12] In particular, NALP-1 predisposes people to vitiligo as well as to various autoimmune diseases. [13] However, certain triggers (e.g., trauma to the skin, hormonal changes, and stress) [14] [15] may be necessary for the disease to become apparent. [5] Autoimmune mechanisms are thought to be responsible in the pathogenesis of vitiligo (especially in generalised or focal non-dermatomal vitiligo). [16] This is supported by an increased incidence of antibodies found in people with vitiligo. [17] Furthermore, vitiligo is often associated with autoimmune diseases, such as thyroid diseases, pernicious anaemia, and diabetes mellitus. [18] Another indication that vitiligo may be caused by an autoimmune mechanism is that melanocyte antibodies have been found in people with vitiligo, and their incidence correlates with disease activity. [19] [20] Involvement

of cellular immunity has been considered because T lymphocytes and macrophages in peri-lesional skin have also been frequently reported. [21] [22] Regarding segmental vitiligo, the neural hypothesis [16] suggests that it is caused by an accumulation of a neurochemical substance, which decreases melanin production.

PROGNOSIS

Vitiligo is not life threatening and is mostly asymptomatic, although it does increase the risk of sunburn of the affected areas due to the absence of melanocytic photo-protection. The association of vitiligo and skin cancer remains an area of controversy. The occurrence of skin cancer in long-lasting vitiligo is rare, [23] although studies have demonstrated increased PUVA-associated skin cancers. A Swedish study [24] that followed up people treated with PUVA over 21 years for a range of benign skin conditions demonstrated an increased risk of squamous cell carcinomas. Furthermore, the risk of malignant melanoma increases among people treated with PUVA by approximately 15 years after the first treatment. [25] The effects of vitiligo can be both cosmetically and psychologically devastating, [26] resulting in low self-esteem [27] and poor body image. [28] The anxieties regarding the disease exist against a background of a lack of understanding of the aetiology and unpredictability of the course. [5] **Progression** The course of generalised vitiligo is unpredictable; lesions may remain stable for years or (more commonly) may progress alternating with phases of stabilisation, or (less commonly) may slowly progress for several years to cover the entire body surface. [29] In some instances, people may undergo rapid, complete depigmentation within 1 or 2 years. [30] In segmental vitiligo, lesions tend to spread rapidly at onset and show a more stable course thereafter. [31] **Predicting treatment responsiveness** Certain disease characteristics help predict the outcome of treatment. Besides age, duration of disease, localisation, and extent of depigmentation, [32] [33] current disease activity should also be considered during clinical decision making. This is essential in people with vitiligo vulgaris, when the disease activity may fluctuate at a given time. Medical therapies and ultraviolet light treatments may be equally effective in active and stable disease. [34] Surgical therapies can be effective interventions for vitiligo, but are limited by the fact that they are invasive and require significant training and expertise to be performed successfully. [35] Surgical treatments are contraindicated in patients who have a history of hypertrophic or keloid scars. An associated skin manifestation is the phenomenon of koebnerisation, [36] [37] [38] [39] where pressure or friction on the skin can cause new lesions or worsen existing ones. Koebnerisation occurs in most people with vitiligo, [4] [40] [41] but elimination of frictional trauma, in the form of occlusive garments and jewellery, prevents occurrence of new lesions in the cosmetically important areas in cases of progressive vitiligo. Also, it has been reported that the presence of positive experimentally induced Koebner phenomenon is associated with active disease, but not necessarily more severe disease (that is, in terms of the extent of depigmentation). [42] The presence of Koebner phenomenon may be a valuable clinical factor for assessing disease activity, and may predict responsiveness to certain treatments. A case series [42] reported that people who were Koebner phenomenon-positive (induced experimentally) were significantly more responsive to topical fluticasone propionate combined with UVA therapy; but, for narrowband UVB treatment, there was no difference in response, suggesting that people in active and stable stages of the disease may respond equally well to UVB.

AIMS OF INTERVENTION

To prevent formation of new skin lesions of the vitiligo; to achieve re-pigmentation of involved skin, thus improving the quality of life, with minimal adverse effects.

OUTCOMES

Treatment success (re-pigmentation) the degree of re-pigmentation that defines success has been arbitrarily set in many studies as 50% to 75% re-pigmentation, based largely on the global impression of the overall response. [43] **Disease progression**, including development of new lesions and arrest of vitiligo spread. There is currently no validated quantitative scale that allows vitiligo to be characterised parametrically, but a model was developed in one RCT [44] of a novel parametric tool, which, if used by clinicians, could provide a more quantifiable comparison of the effects of different interventions. **Quality of life** measured using a validated tool. **Adverse effects**.

METHODS

BMJ Clinical Evidence search and appraisal April 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to April 2014, Embase 1980 to April 2014, and The Cochrane Database of Systematic Reviews, issue 4, 2014 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts of the studies identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were published RCTs and systematic reviews of RCTs in the English language, any level of blinding, and containing at least 20 individuals (at least 10 per arm), of whom at least 80% were

followed up. There was no minimum length of follow-up. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 16). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of surgical treatments for vitiligo in adults and children?**

OPTION **BLISTER GRAFTS** New

- For GRADE evaluation of interventions for Vitiligo in adults and children: surgical interventions, see table, p 16 .
- We do not know whether blister grafts are effective compared with placebo/no treatment or the other surgical interventions included in this review for people with vitiligo, as we found insufficient evidence from RCTs.

Benefits and harms

Blister grafts versus placebo or no treatment:

We found no systematic review or RCTs.

Blister grafts versus split thickness skin grafts:

We found two systematic reviews (search dates 2009; [5] and 2013 [35]), which both identified the same RCT.

Treatment success

Blister grafts versus split-thickness skin grafts We don't know how blister grafts and split-thickness skin grafts compare at increasing re-pigmentation (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Re-pigmentation					
[35] Systematic review	20 people (aged 10–49 years) with generalised vitiligo for at least 1 year with patches on body sites not exposed to the sunlight Data from 1 RCT	**Proportion showing re-pigmentation , 3 months** 45% with blister grafts 65% with split-thickness grafts Absolute numbers not reported This outcome was not reported in the first systematic review, as the study did not assess the proportion of people with >50% or 75% re-pigmentation [5]	Not reported		

Disease progression

No data from the following reference on this outcome. [5] [35]

Quality of life

No data from the following reference on this outcome. [5] [35]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[5] Systematic review	20 people (aged 10–49 years) with generalised vitiligo for at least 1 year with patches on body sites not exposed to the sunlight Data from 1 RCT	**Adverse effects** with blister grafts with skin-thickness skin grafts Overall adverse effects reported with no breakdown by treatment group: Koebner phenomenon (n = 19), hypopigmentation (n = 14), hyperpigmentation (n = 3), scarring (n = 7) and infection (n = 3) at the donor sites; and milia (n = 4), pigment loss (n = 8), papules (n = 19), peripheral hypopigmentation (n = 2), scarring (n = 1), and infection (n = 6) at the recipient sites			

Blister grafts versus non-cultured cellular transplantation:

We found two systematic reviews (search dates 2009; [5] and 2013 [35]), which found no RCTs. We found one additional RCT. [45]

Treatment success

Blister grafts versus non-cultured cellular transplantation Non-cultured cellular transplantation may be more effective than blister grafts at increasing re-pigmentation at 16 weeks when undertaken in combination with variable daily sunlight exposure; however, the result varied with the analysis used and this is based on one small RCT (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Re-pigmentation					
[45] RCT	41 people (12–40 years, 54 lesions) with stable vitiligo for at least 1 year not responding to medical therapy	**Re-pigmentation 90%–100% , 16 weeks** 7/26 (27%) lesions with blister grafts (20 people) 20/28 (71%) lesions with non-cultured cellular transplantation (21 people) All participants were asked to expose the areas to sunlight from 5–30 minutes daily	P = 0.002	○○○	non-cultured cellular transplantation
[45] RCT	41 people (12–40 years, 54 lesions) with stable vitiligo for at least 1 year not responding to medical therapy	**Re-pigmentation at least 75% , 16 weeks** 22/26 (85%) lesions with blister grafts (20 people) 25/28 (89%) lesions with non-cultured cellular transplantation (21 people)	P = 0.61	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		All participants were asked to expose the areas to sunlight from 5–30 minutes daily			

Disease progression

No data from the following reference on this outcome. [45]

Quality of life

Blister grafts versus non-cultured cellular transplantation Non-cultured cellular transplantation may be more effective than blister grafts at improving quality of life at 16 weeks; however, this is based on one small RCT (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[45] RCT	41 people (12–40 years, 54 lesions) with stable vitiligo for at least 1 year not responding to medical therapy	**Mean reduction from baseline in quality of life (assessed using Dermatology Life Quality Index) , 16 weeks** 6.80 with blister grafts 9.12 with non-cultured cellular transplantation All participants were asked to expose the areas to sunlight from 5–30 minutes daily	P = 0.045	○○○	non-cultured cellular transplantation

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hyperpigmentation					
[45] RCT	41 people (12–40 years, 54 lesions) with stable vitiligo for at least 1 year not responding to medical therapy	**Hyperpigmentation , 16 weeks** 3/26 (12%) lesions with blister grafts (20 people) 4/28 (14%) lesions with non-cultured cellular transplantation (21 people) No patients in either groups developed infection, scarring or milia at either the donor or recipient sites; see Further information on studies	Not reported		
Hypopigmentation					
[45] RCT	41 people (12–40 years, 54 lesions) with stable vitiligo for at least 1 year not responding to medical therapy	**Hypopigmentation , 16 weeks** 5/26 (19%) lesions with blister grafts (20 people) 2/28 (7%) lesions with non-cultured cellular transplantation (21 people) The study reported that the lesions that showed hypopigmenta-	Not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		tion had "a tendency to match the normal skin colour over time"; see Further information on studies			

Further information on studies

[45] All participants were asked to expose the areas to sunlight from 5 to 30 minutes daily. The study was conducted in India.

Comment: It is important to remember that, in studies using sunlight as the source of UVA variable factors (compliance, degree of sun exposure, country where the trial was conducted) can limit the interpretation and applicability of results.

Clinical guide
Non-cultured cellular transplantation could be used in adolescents and adults to treat stable vitiligo that is unresponsive to medical therapies.

OPTION CULTURED CELLULAR TRANSPLANTATION New

- For GRADE evaluation of interventions for Vitiligo in adults and children: surgical interventions, see table, p 16 .
- We don't know how cultured cellular transplantation compares with no active treatment or with other surgical interventions, as we found no RCTs.

Benefits and harms

Cultured cellular transplantation versus placebo:

We found two systematic reviews (search dates 2009; [5] and 2013 [35]), which found no RCTs.

Cultured cellular transplantation versus other surgical interventions:

We found no systematic review or RCTs.

Comment: Cultured cellular transplantation requires laboratory equipment and expertise, which is thought to enhance the efficacy of transplanted melanocytes in vitiligo. The percentage of re-pigmentation has been reported in prospective studies to range from 75% to 84% in patients with focal or stable vitiligo and between 30% to 54% in those with generalised vitiligo. [46] [47]

Clinical guide
There are no RCTs to provide guidance for clinical use of cultured cellular transplants.

OPTION NON-CULTURED CELLULAR TRANSPLANTATION New

- For GRADE evaluation of interventions for Vitiligo in adults and children: surgical interventions, see table, p 16 .
- The evidence for non-cultured cellular transplantation is limited and we found no studies assessing non-cultured cellular transplantation alone.

- Non-cultured cellular transplantation plus ultraviolet light may be more effective than placebo plus ultraviolet light at increasing re-pigmentation at 12 months. However, this is based on one small RCT.

Benefits and harms

Non-cultured cellular transplantation plus ultraviolet light versus placebo plus ultraviolet light:

We found two systematic reviews (search dates 2009; [5] and 2013 [35]), which both identified the same RCT [48] but as they do not report the results in much detail, data have been extracted directly from the RCT.

Treatment success

Non-cultured cellular transplantation plus ultraviolet light versus placebo plus ultraviolet light Non-cultured cellular transplantation may be more effective than placebo when used in conjunction with UV light at increasing re-pigmentation at 12 months; however, this is based on one small RCT (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Re-pigmentation					
[48] RCT	28 people (aged 15–65 years) with vitiligo (19 with clinically stable vitiligo defined as no progression in previous 12 months, and 9 with indications of disease activity) In review [5] [35]	**Re-pigmentation , 12 months** with non-cultured cellular transplantation with placebo Absolute results not reported Both arms received PUVA or UV irradiation twice-weekly for 2 months, commencing 3 weeks after the procedure	P = 0.002	○○○	non-cultured cellular transplantation

Disease progression

No data from the following reference on this outcome. [48]

Quality of life

No data from the following reference on this outcome. [48]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hyperpigmentation					
[48] RCT	28 people (aged 15–65 years) with vitiligo (19 with clinically stable vitiligo defined as no progression in previous 12 months, and 9 with indications of disease activity) In review [5] [35]	**Hyperpigmentation , 12 months** with non-cultured cellular transplantation with placebo Hyperpigmentation was observed in 5 responding lesions for approximately 6 months; in all other responding lesions, colour match was immediately good The RCT reported that no scars were observed in the recipient areas	Not reported		

Non-cultured cellular transplantation versus blister grafts:
See option on Blister grafts, p 4 .

Further information on studies

[48] In this RCT, non-cultured cellular transplantation consisted of melanocyte medium, hyaluronic acid, and epidermal cells, while the placebo group received only the melanocyte medium and hyaluronic acid. Each participant received treatment and placebo interventions on different lesions. Moreover, four participants received treatment and placebo at four sites in total. No lesions on the face or neck were included in this study. The mean surface area of lesions was 2.8 cm^2 for actively treated lesions (range 0.2–8.9 cm^2); and 2.9 cm^2 for the placebo treated lesions (range 0.6– 8.1 cm^2). Three weeks after the procedure, all patients received UVB irradiation or PUVA twice-weekly for 2 months. The method for allocation to the different types of UV treatment and responses according to the different types of post-procedure UV therapy was not reported in the RCT. Significant differences in re-pigmentation in favour of non-cultured cellular transplantation were also reported between lesions treated with non-cultured cellular transplantation and those treated with placebo at 3 months (P <0.001) and 6 months (P = 0.002). Only three participants in the placebo-treated sites experienced re-pigmentation in at least 20% of the area. In two out three of these, it was suggestive of post-inflammatory pigmentation. The study was conducted in Belgium.

Comment: The safe duration of narrowband UVB and maximum cumulative dose compared with other treatment modalities remains undetermined, but the consensus is that this form of treatment is safe and effective in children, and may improve their quality of life. [49] UVB phototherapy has the advantage of not requiring photo-protective goggles post-treatment. Furthermore, there is consensus that the risk of developing skin cancers from light treatments is lowest with narrowband UVB and highest with PUVA. In general, PUVA is not recommended for children under the age of 12 years.

Clinical guide
Non-cultured cellular transplantation can be used to treat reasonably small-sized areas of stable vitiligo in both children and adults. However it has the potential to treat larger areas (up to 10 times the donor area), without the need for cell cultures. This treatment does, however, require laboratory support. Long-term results are lacking.

OPTION PUNCH/MINI GRAFTS New

- For GRADE evaluation of interventions for Vitiligo in adults and children: surgical interventions, see table, p 16 .
- The evidence for mini-punch grafts is limited and we found no studies assessing punch/mini grafts alone or comparing them with no active treatment.
- Mini-punch grafts plus PUVAsol may not be as effective as split thickness skin grafts plus PUVAsol at increasing re-pigmentation at 3 months; however, we don't know about long-term re-pigmentation, and this is based on one small RCT.
- It should be noted that, in general, PUVA is not recommended for children under the age of 12 years. Results from studies including PUVA as an intervention carried out in mixed-age groups should not be extrapolated to children.
- Larger areas of vitiligo can be treated using split-thickness skin grafts compared with mini-punch grafts, but this may be at the cost of increased adverse effects (with the exception of graft failure). Graft rejection in mini-punch grafts is higher than that reported for split-thickness skin grafts. Other possible adverse events of mini-punch grafts include cobblestoning of the graft and poor cosmesis.
- In clinical practice, size of lesions of vitiligo and extent of area involved will determine choice of grafting.

Benefits and harms

Punch/mini grafts versus placebo or no treatment:

We found no systematic reviews or RCTs.

Punch/mini grafts plus PUVAsol versus split-thickness skin grafts plus PUVAsol:

We found two systematic reviews (search dates 2009; [5] and 2013 [35]), which both identified the same RCT.

Treatment success

Punch/mini grafts plus PUVAsol versus split-thickness skin grafts plus PUVAsol Split-thickness skin grafts plus PUVAsol may be more effective than mini-punch grafts plus PUVAsol at increasing re-pigmentation at 3 months; however, we do not know if they are more effective in the longer term, and this is based on one small RCT (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Re-pigmentation					
[5] Systematic review	64 adults and children (aged 10–42 years) with stable localised vitiligo for 1–18 years with lesions resistant to conventional medical therapy and remaining unchanged (no progression or regression) for at least 6 months Data from 1 RCT	**Proportion showing re-pigmentation (>75%) , 3 months** 15/34 (44%) with mini-punch grafts 25/30 (83%) with split-thickness skin grafts Both arms received PUVAsol on alternate days, 2 weeks after the graft See Further information on studies	RR 1.89 95% CI 1.25 to 2.85 P value not reported	●○○	split-thickness skin grafts

Disease progression

No data from the following reference on this outcome. [5] [35]

Quality of life

No data from the following reference on this outcome. [5] [35]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hypertrophic scarring					
[5] Systematic review	64 adults and children (aged 10–42 years) with stable localised vitiligo for 1–18 years with lesions resistant to conventional medical therapy and remaining un-	**Hypertrophic scarring , 3 months** 0/34 (0%) with mini-punch grafts 3/30 (10%) with split-thickness skin grafts Both arms received PUVAsol on alternate days, 2 weeks after the	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	changed (no progression or regression) for at least 6 months Data from 1 RCT	graft; see Further information on studies			
Rejection of grafts					
[35] Systematic review	797 grafts in 64 people (aged 10–42 years) with stable localised vitiligo for 1–18 years with lesions resistant to conventional medical therapy and remaining unchanged (no progression or regression) for at least 6 months Data from 1 RCT	**Graft rejection , 3 months** 81/644 (13%) with mini-punch grafts (n = 34) 7/153 (5%) with split-thickness skin grafts (n = 30) In the split-thickness skin grafts arm, 1 person had 7 graft rejections; it was not reported how many individuals had rejection of grafts in the mini-punch group Both arms received PUVAsol on alternate days, 2 weeks after the graft; see Further information on studies	Not reported		
Graft depigmentation					
[5] Systematic review	64 adults and children (aged 10–42 years) with stable localised vitiligo for 1–18 years with lesions resistant to conventional medical therapy and remaining unchanged (no progression or regression) for at least 6 months Data from 1 RCT	**Graft depigmentation , 3 months** 0/34 (0%) with mini-punch grafts 2/30 (7%) with split-thickness skin grafts Both arms received PUVAsol on alternate days, 2 weeks after the graft; see Further information on studies	Not reported		
Graft contracture					
[5] Systematic review	64 adults and children (aged 10–42 years) with stable localised vitiligo for 1–18 years with lesions resistant to conventional medical therapy and remaining unchanged (no progression or regression) for at least 6 months Data from 1 RCT	**Graft contracture , 3 months** 0/34 (0%) with mini-punch grafts 2/30 (10%) with split-thickness skin grafts Both arms received PUVAsol on alternate days, 2 weeks after the graft; see Further information on studies	Not reported		
Milia formation					
[5] Systematic review	64 adults and children (aged 10–42 years) with stable localised vitiligo for 1–18 years with lesions resistant to conventional medical therapy and remaining unchanged (no progression or regres-	**Milia formation , 3 months** 0/34 (0%) with mini-punch grafts 4/30 (13%) with split-thickness skin grafts Both arms received PUVAsol on alternate days, 2 weeks after the graft; see Further information on studies	Not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	sion) for at least 6 months Data from 1 RCT				
Achromic fissuring					
[5] Systematic review	64 adults and children (aged 10–42 years) with stable localised vitiligo for 1–18 years with lesions resistant to conventional medical therapy and remaining unchanged (no progression or regression) for at least 6 months Data from 1 RCT	**Achromic fissuring , 3 months** 0/34 (0%) with mini-punch grafts 4/30 (13%) with split-thickness skin grafts Both arms received PUVAsol on alternate days, 2 weeks after the graft; see Further information on studies	Not reported		
Cobblestoning					
[5] Systematic review	64 adults and children (aged 10–42 years) with stable localised vitiligo for 1–18 years with lesions resistant to conventional medical therapy and remaining unchanged (no progression or regression) for at least 6 months Data from 1 RCT	**Cobblestoning , 3 months** 7/34 (21%) with mini-punch grafts 0/30 (0%) with split-thickness skin grafts Both arms received PUVAsol on alternate days, 2 weeks after the graft; see Further information on studies	Not reported		

Further information on studies

[5] The people included in the RCT ranged from 10 to 42 years old with a mean age of 19.9 years in the mini-punch graft arm and 22.6 years in the split thickness skin graft arm. In the mini-punch graft group, 2.5 mm grafts were obtained from the upper thigh after infiltrating the area with 2% lignocaine without adrenaline. The grafts were then transplanted to the depigmented areas, from which similar-sized circles of skin had been removed. In the split-thickness skin grafts group, the grafts were obtained from the thigh region after scrutiny for scars, striae, or infection. The split-thickness grafts ranged from approximately 1 to 18 cm^2. After 2 weeks, once the grafts were accepted, the participants underwent PUVAsol therapy (oral psoralen, followed 2 hours later by sun exposure) on alternate days for 3 months. The study was conducted in India.

Comment:

PUVA (oral) treatment duration Long-term therapy is needed for successful re-pigmentation of vitiliginous skin. Between 15 and 25 treatments are necessary before perifollicular re-pigmentation is apparent. Between 100 and 300 treatments are required for complete re-pigmentation of the neck, trunk, and proximal limbs, with the face re-pigmenting faster. At 4 years' follow-up, people neither developed cutaneous malignancies nor developed abnormal liver function values. [50]

UVA source It is important to remember that, in studies using sunlight as the source of UVA, [50] [51] variable factors (compliance, degree of sun exposure, country where the trial was conducted) can limit the interpretation and applicability of results. Where possible, reliable forms of light therapy such as UV light devices should be used in trials, but this is not always accessible or feasible in resource-poor countries. No RCTs have been carried out using different UVA light devices.

PUVA in children In general, PUVA is not recommended for children under the age of 12 years. [33] Results from studies including PUVA as an intervention carried out in mixed-age groups should

not be extrapolated to children. The phototoxic potential of psoralens is of great concern in children, where avoidance of excessive sun exposure may be difficult to regulate. PUVA therapy is not advocated in children under the age of 12 years because of the risk of cataract formation (because the eye is not fully developed until the age of 12 years) and because of the increased risk of skin cancer.

Clinical guide

Mini-punch grafts plus PUVAsol are less effective than split-thickness skin graft plus PUVAsol at increasing re-pigmentation in the short term. Larger areas of vitiligo can be treated using split-thickness skin grafts, but at the cost of increased adverse effects (with the exception of graft failure). Size of lesions of vitiligo and extent of area involved will determine choice of grafting.

OPTION SPLIT-THICKNESS SKIN GRAFTS New

- For GRADE evaluation of interventions for Vitiligo in adults and children: surgical interventions, see table, p 16 .
- The evidence for split-thickness skin grafts is limited. We found no studies assessing split thickness skin grafts compared with no active treatment, and we found only one small RCT of split thickness skin grafts alone, which compared them with blister grafts.
- Split-thickness skin grafts plus PUVAsol may be more effective than mini-punch grafts plus PUVAsol at increasing re-pigmentation at 3 months; however, we don't know about longer term re-pigmentation.
- Split-thickness skin grafts can be used to treat large areas of vitiligo. However, they may incur significant side effects, including milia formation, graft contractures, graft depigmentation, and achromic fissuring.

Benefits and harms

Split-thickness skin grafts versus placebo or no treatment:

We found no systematic review or RCTs.

Split-thickness skin grafts versus blister grafts:

See option on Blister grafts, p 4 .

Split-thickness skin grafts plus PUVAsol versus punch/mini grafts plus PUVAsol:

See option on Punch/mini grafts, p 9 .

Comment: In studies using sunlight as the source of UVA variable factors (compliance, degree of sun exposure, country where the trial was conducted) can limit the interpretation and applicability of results. Where possible, reliable forms of light therapy such as UV light devices should be used in trials, but this is not always accessible or feasible in resource-poor countries.

Clinical guide

Split-thickness skin grafts plus PUVAsol are more effective than mini-punch grafts plus PUVAsol at increasing re-pigmentation in the short term. Larger areas of vitiligo can be treated using split-thickness skin grafts, but at the cost of increased adverse effects (with the exception of graft failure). Size of lesions of vitiligo and extent of area involved will determine choice of grafting.

GLOSSARY

Active vitiligo An extending vitiligo with enlarging lesions or development of new lesions.

Koebner phenomenon The development of vitiligo at sites of aspecifically traumatised skin.

Localised vitiligo can consist either of focal lesions (macules appear in a non-dermatomal distribution) or a segmental form (macules are localised in a segmental distribution that is frequently not dermatomal, commonly seen in children).

Vitiligo vulgaris A symmetrical type of generalised vitiligo in which scattered macules are seen over the entire body.

Generalised vitiligo Characterised by multiple scattered lesions in a symmetrical distribution pattern. It occurs in acrofacial, periorifacial, and orifacial types, in which the distal extremities and face are involved. In the universal form, there is more than 80% depigmentation.

Low-quality evidence 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.

Narrowband ultraviolet B 310 nm to 315 nm wavelength ultraviolet radiation.

PUVA Combination therapy of ultraviolet A and topical or oral psoralen. The psoralen sensitises the skin to ultraviolet A and is taken or is applied a set period of time before the ultraviolet A exposure.

PUVAsol A combination topical or oral psoralen with natural sunlight exposure.

Parametrically A set of measurable factors that define a condition and determine its course which are varied in a trial.

Segmental vitiligo A form of localised vitiligo where one or more lesions of vitiligo can arise.

Ultraviolet A 315 nm to 400 nm ultraviolet radiation.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Blister grafts New option. Two systematic reviews [5] [35] and one additional RCT [45] added. Categorised as 'unknown effectiveness'.

Cultured cellular transplantation New option. Two systematic reviews added. [5] [35] Categorised as 'unknown effectiveness'.

Non-cultured cellular transplantation New option. Two systematic reviews added [5] [35] and one RCT. [48] Categorised as 'unknown effectiveness'.

Punch/mini grafts New option. Two systematic reviews added. [5] [35] Categorised as 'unknown effectiveness'.

Split-thickness skin grafts New option. Two systematic reviews added. [5] [35] Categorised as 'unknown effectiveness'.

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GRADE **Evaluation of interventions for Vitiligo in adults and children: surgical interventions.**

Important outcomes			Disease progression, Quality of life, Treatment success						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of surgical treatments for vitiligo in adults and children?									
1 (20) [5] [35]	Treatment success	Blister grafts versus split thickness skin grafts	4	–2	0	–1	0	Very low	Quality point deducted for sparse data and absolute numbers not reported; directness point deducted for applicability of results
1 (41) [45]	Treatment success	Blister grafts versus non-cultured cellular transplantation	4	–1	–1	–1	0	Very low	Quality point deducted for sparse data; consistency point deducted for different results depending on outcome measured; directness point deducted for use of co-intervention
1 (41) [45]	Quality of life	Blister grafts versus non-cultured cellular transplantation	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for use of co-intervention
1 (28) [48]	Treatment success	Non-cultured cellular transplantation plus ultraviolet light versus placebo plus ultraviolet light	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and absolute numbers not reported; directness points deducted for applicability of results and use of co-intervention
1 (64) [5] [35]	Treatment success	Punch/mini grafts plus PUVAsol versus split-thickness skin grafts plus PUVAsol	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for use of co-intervention

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.