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[Intervention Review]

Psychological therapies for thalassaemia

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ABSTRACT

Background

Thalassaemia is a group of genetic blood disorders characterised by the absence or reduction in the production of haemoglobin. Severity is variable from less severe anaemia, through thalassaemia intermedia, to profound severe anaemia (thalassaemia major). In thalassaemia major other complications include growth retardation, bone deformation, and enlarged spleen. Blood transfusion is required to treat severe forms of thalassaemia, but this results in excessive accumulation of iron in the body (iron overload), removed mostly by a drug called desferrioxamine through 'chelation therapy'. Non-routine treatments are bone marrow transplantation (which is age restricted), and possibly hydroxyurea, designed to raise foetal haemoglobin level, thus reducing anaemia. In addition, psychological therapies seem appropriate to improving outcome and adherence to medical treatment.

Objectives

To examine the evidence that in people with thalassaemia, psychological treatments improve the ability to cope with the condition, and improve both medical and psychosocial outcomes.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Haemoglobinopathies Trials Register which comprises of references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings. Searches on the Internet were also performed.

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 11 November 2013.

Selection criteria

All randomised or quasi-randomised controlled trials comparing the use of psychological intervention to no (psychological) intervention in people with thalassaemia.

Data collection and analysis

No trials of psychological therapies have been found in the literature for inclusion in this review.

Main results

There are currently no results to be reported.

Authors' conclusions

As a chronic disease with a considerable role for self-management, psychological support seems appropriate for managing thalassaemia. However, from the information currently available, no conclusions can be made about the use of specific psychological therapies in thalassaemia. This systematic review has clearly identified the need for well-designed, adequately-powered, multicentre, randomised controlled trials assessing the effectiveness of specific psychological interventions for thalassaemia.

PLAIN LANGUAGE SUMMARY

Using psychological treatments to help people manage thalassaemia

Thalassaemia is a group of genetic blood disorders. Blood transfusion is needed to treat severe forms of the condition, but this results in a high level of iron in the body. This excess iron is usually removed by drugs through 'chelation therapy'. Other less usual treatments are bone marrow transplantation, which is restricted by age, and hydroxyurea, a drug designed to raise the level of foetal haemoglobin and reduce anaemia. Psychological support would seem suitable to manage thalassaemia which is a chronic disease with a considerable role for self-management. We were not able to find any trials to include in this review. There are some reports that teaching people about their condition improves adherence to chelation therapy. However, from the information currently available, we can not recommend the use of specific psychological therapies in thalassaemia. We believe there is a need for large trials to assess the value of psychological therapies for thalassaemia.

BACKGROUND

Description of the condition

Thalassaemia syndromes are a family of genetic blood disorders characterised by an imbalance in the synthesis of globin chains, which may result in the absence or reduction of the production of adult haemoglobin. The major component found in adult red blood cells is haemoglobin A, which consists of two alpha and two beta protein 'globin' chains ($\alpha^2\beta^2$) combined with 'haem' containing iron. The minor haemoglobin is A_2 , which consists of two alpha and two delta globin chains ($\alpha^2\delta^2$). Foetal haemoglobin (which declines after birth) is also present and consists of two alpha and two gamma globin chains ($\alpha^2\gamma^2$). Several hundreds of different mutations or deletions of globin genes have been found, that may give rise to different forms of thalassaemia. Alpha thalassaemia and beta thalassaemia are the most common and clinically relevant.

Alpha thalassaemia is the loss of alpha globin chains. Alpha genes are duplicated and usually depicted as ($\alpha\alpha/\alpha\alpha$). Loss of both genes is called α^0 thalassaemia, represented as ($--/\alpha\alpha$), and loss of one gene is called α^+ thalassaemia i.e. ($-\alpha/\alpha\alpha$). Usually these alpha genes are lost by deletion, less commonly by mutation. Foetal haemoglobin and adult haemoglobin have alpha globin chains, therefore the condition is found in both foetal and adult life. In addition to the reduced haemoglobin formation caused by decreased production of alpha globin chains, there is an excess of gamma globin and beta globin chains leading to haemoglobin Bart's (gamma globin tetramers) and haemoglobin H (beta globin tetramers). Severity varies according to the type of defect.

By contrast, beta thalassaemia results from different mutations of beta globin genes leading to the absence of beta globin chains (β^0 thalassaemia) or their reduced synthesis (β^+ thalassaemia), with an excess of alpha globin chains. Severity is also variable from mild anaemia, through intermediate forms, to severe anaemia. In severe cases of beta thalassaemia (known as thalassaemia major) other complications include bone deformation, enlarged spleen, and growth retardation (Weatherall 1997).

Thalassaemia is found across the world. Affected population estimated rates are: Europe 0.9%; Asia 4.1%; Africa 13.3%; Oceania (including Australia, New Zealand, Papua New Guinea and Fiji) 1.3%; and the Americas 2% (WHO 1994). In many populations where thalassaemia is common, the genes for haemoglobin variants such as the sickle haemoglobin S, or haemoglobin C and E are also prevalent. Therefore, some people inherit a gene for beta thalassaemia from one parent and a gene for haemoglobin variant from the other. The most important diseases of this type are sickle beta thalassaemia and haemoglobin E beta thalassaemia. Over 4.5% of the global population carry a haemoglobin variant gene. However, almost three-quarters of affected births are in Africa (WHO 1994).

Phenotype classification of thalassaemia is based on severity of anaemia and need for transfusion therapy. Carriers with only one abnormal gene have thalassaemia minor (mild anaemia with minor haematological changes). People with two or more abnormal genes may inherit thalassaemia intermedia (moderate anaemia with typical body alterations (e.g. bone deformation, growth retardation) or thalassaemia major (severe transfusion-dependent anaemia). Life-long and regular blood transfusion is

required to treat thalassaemia major. This results in excessive accumulation of iron in the body (iron overload), which in the long term leads to severe clinical complications, such as heart and liver failure, diabetes and hypogonadism (Weatherall 1997). Iron overload may be prevented and treated by daily removal (iron chelation therapy), which involves overnight infusions of desferrioxamine (Desferal®). Poor compliance with this treatment is the most common clinical problem in thalassaemia major (Brittenham 1994). Alternative chelating agents, including oral deferiprone, are under study and may be less safe and effective (Olivieri 1995). Due to advances in transfusion regimens, chelation therapy, and the treatment of the complications of thalassaemia, many people with thalassaemia can lead active lives and have increased survival (Modell 2000). Many of these people are now treated as outpatients and in peripheral centres. Other treatments are bone marrow transplantation, which is limited to those with a sibling of the same tissue type (Lucarelli 1993), and hydroxyurea (which is currently under study), a drug which may raise foetal haemoglobin level in a small proportion of cases (Arruda 1997).

Psychosocial problems associated with thalassaemia include feelings of distress; poor social functioning, such as integration into school and work (Masera 1990); and expression of guilt, denial and over-protectiveness of families (Massaglia 1985). A descriptive study suggests that psychosocial burden is associated with clinical severity (Ratip 1995). Adherence to iron chelation therapy is a major issue (especially in adolescents with thalassaemia), such that some behavioural interventions focus on the self-management of chelation.

Description of the intervention

The object of psychological therapies are to help people with thalassaemia cope better, fulfil roles, and to achieve better quality of life. These interventions are age-appropriate, and usually available in both hospital and community based settings.

Psychological therapies for managing thalassaemia include patient education, cognitive therapy, behavioural therapy and psychodynamic psychotherapy. Specific examples of each of these are given below in 'Types of interventions'.

How the intervention might work

Psychological interventions, if effective, will lead to acquisition or improvement of effective coping strategies to alleviate symptoms and emotional difficulties. Individuals will see a reduction in emotional distress, have more positive moods, better adhere to medical treatment (including iron chelation), and show an improved quality of life.

Why it is important to do this review

This Cochrane Review is an update of one originally published in 2001 (Anie 2001). The review examines the contribution of psychological interventions used for managing thalassaemia (major and intermediate), transfusion therapy and iron chelation therapy; it also considers the relative efficacy of different therapy formats (e.g. individual versus group) for managing iron chelation therapy in thalassaemia.

OBJECTIVES

The purpose of this review was to examine whether psychological therapies for thalassaemia can improve the ability of individuals to cope with their condition, and to self-manage iron chelation. There were two main objectives.

1. To determine whether psychological therapies are effective in the management of:
 - a. the disease;
 - b. transfusion therapy;
 - c. iron chelation therapy.
2. To determine which psychological intervention as described under '[Types of interventions](#)' is most effective for managing iron chelation in thalassaemia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised trials. Trials in which quasi-randomised methods, such as alternation, are used were included if there was sufficient evidence that the treatment and control groups were similar at baseline.

Types of participants

All children and adults diagnosed with beta thalassaemia (major and intermediate), irrespective of phenotype, severity, age, gender and ethnic origin.

Types of interventions

This review focuses on four main types of psychological interventions. All trials that included one or more of the following therapies for managing psychological problems, and iron chelation in thalassaemia were considered.

Patient Education

1. Thalassaemia
2. Chronic blood transfusions
3. Iron chelation therapy

Cognitive Therapy

1. Focus on ways of thinking, i.e. automatic thoughts or self-statements and negative thoughts
2. Monitoring thoughts and feelings
3. Challenging and re-framing inappropriate thoughts
4. Attention diversion and distraction
5. Imagery and hypnosis

Behavioural Therapy

1. Activity monitoring and re-scheduling
2. Stress monitoring and reduction
3. Relaxation therapy and biofeedback
4. Communication skills training including assertiveness training
5. Goal setting
6. Enhancing motivation
7. Problem solving

Psychodynamic Psychotherapy

1. Focus on childhood development and early life experiences
2. Insight into previous traumatic events

Types of outcome measures

The following outcomes in people with thalassaemia were agreed upon for the review. Relevant trials identified need to include at least one of the following:

Primary outcomes

1. Mood (anxiety, depression)
2. Coping strategies (behavioural responses, cognitive strategies)
3. Medical outcomes (serum ferritin, body iron load (including cardiac and liver iron)), split and analysed separately by severity of thalassaemia:
 - a. thalassaemia major (those on regular transfusions (four-weekly or more often))
 - b. thalassaemia intermedia (those on transfusions intermittently or occasionally)

Secondary outcomes

1. Health service utilisation (frequency of emergency department visits and hospital admissions, duration of hospitalisations, consultations with doctors (including general practitioners))
2. Quality of life (physical and social function, ability to fulfil roles, life satisfaction)
3. Health beliefs (locus of control)
4. General health (including mental health)

We planned to group the outcomes into time periods: short-term (up to three months); medium-term (between three months and six months); and long-term (over six months) as appropriate.

Search methods for identification of studies

Electronic searches

Relevant trials were identified from the Group's Haemoglobinopathies Trials Register using the terms: (education* OR psycholog*) AND thalassaemia.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*) and quarterly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the [Cochrane Cystic Fibrosis & Genetic Disorders Group Module](#).

We also searched Embase (1974 to 2014 Week 04), Biological Abstracts (1982 to 1995), PsycLIT (1974 to July 2003), PsycINFO (1967 to January week 3 2014), CINAHL (1983 to July 2003), SciSearch - Social Science Citation Index, and Google Scholar.

For the full search strategies employed, please see the additional tables attached to this review ([Appendix 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#)).

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 11 November 2013.

Searching other resources

An attempt was also made to identify any unpublished data through contact with experts in the field, and personal communication with known authors.

Data collection and analysis

The process described below was not applied as no trials were identified. However, if trials are included in future updates of this review, the following methods will be applied.

Selection of studies

We will independently select the trials to be included in the review. We will resolve any disagreement through discussion.

Data extraction and management

We will independently extract data using standard data acquisition forms. In cases of uncertainty, another expert in the field will be invited to make an independent assessment based on the selection criteria. If disagreement arises on the suitability of a trial for inclusion in the review or on its quality, we plan to reach a consensus by discussion.

Assessment of risk of bias in included studies

We will assess the risk of bias of each included study using the methods described in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). The dimensions listed below will be assessed.

1. Randomisation (including allocation concealment and blinding)
2. Participant adherence and exclusions
 - a. record of participants lost to follow up or subsequently excluded from the trial
 - b. intention-to-treat analyses
3. Therapists' training and materials
 - a. competence
 - b. credibility of treatment

Measures of treatment effect

For binary outcomes, we will calculate a pooled estimate of the treatment effect for each outcome across trials (the odds of an outcome among treatment allocated participants to the corresponding odds among controls).

For continuous outcomes, we plan to record either mean change from baseline for each group or mean post treatment or intervention values and the standard deviation or standard error for each group. Also, we will calculate a pooled estimate of treatment effect by calculating the weighted mean difference.

Unit of analysis issues

Trials with a cross-over design are unlikely. In the case of cluster randomised trials, we planned to calculate the intra-correlation coefficient (ICC) and design effect ([Bland 2004](#)).

Dealing with missing data

In order to allow an intention-to-treat analysis, authors will seek data on the number of participants by allocated treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up.

Assessment of heterogeneity

We plan to assess the degree of heterogeneity between trials using the I^2 statistic ([Higgins 2003](#)). This measure describes the percentage of total variation across studies that are due to heterogeneity rather than by chance ([Higgins 2003](#)). The values of I^2 lie between 0% and 100%, and a simplified categorization of heterogeneity that we plan to use is of low (I^2 value of 25%), moderate (I^2 value of 50%), and high (I^2 value of 75%) ([Higgins 2003](#)).

Assessment of reporting biases

If we are able to undertake a meta-analysis, we will try to assess publication bias by means of a funnel plot. We will also attempt to identify and report on selective reporting by the primary investigators.

Data synthesis

We plan to use a fixed-effect model to analyse the data; however, if we identify a moderate to high degree of heterogeneity, we will utilize a random-effects model.

Subgroup analysis and investigation of heterogeneity

We plan to conduct, where possible, subgroup analyses for:

1. Age: children (0 to 17 years) versus adults (18 years and over);
2. Setting: hospital versus community.

Sensitivity analysis

A sensitivity analysis based on the methodological quality of the trials, including and excluding quasi-randomised trials is planned.

RESULTS

Description of studies

No randomised controlled trials employing psychological therapies as described in '[Types of interventions](#)' were identified by the literature searches undertaken for this review. Also, no trials, where quasi-randomisation methods such as alternation are used, were found. We plan to analyse these trials separately, but only if there is sufficient evidence that the treatment and non-treatment groups are comparable in terms of clinical features.

Risk of bias in included studies

No trials were assessed.

Effects of interventions

No trials were eligible for inclusion in this review.

DISCUSSION

Suitable trials were not found in the literature for our objectives to be achieved at present. We cannot, at this time, draw any conclusions on the efficacy of psychological therapies for people with thalassaemia to help them adjust and manage their condition. Nonetheless, the literature indicates that patient educational intervention improves adherence to chelation therapy ([Treadwell 2001](#)).

AUTHORS' CONCLUSIONS

Implications for practice

No conclusions can be drawn at the present time about the effectiveness of psychological therapies for managing thalassaemia.

Implications for research

There seems no reason to justify the absence of randomised controlled trials of psychological therapies for thalassaemia, since the need for psychological interventions is indicated in the literature. Also, psychological trials of this nature have been conducted in similar conditions such as sickle cell disease.

Research is needed using a structured approach to the assessment of psychological therapies for thalassaemia, which take into account both demographic and clinical variables. Well-designed, adequately-powered trials should incorporate treatment manuals in identifying the most important components of psychological interventions, relevant to different thalassaemia populations, and in testing the efficacy of different therapy formats, e.g. individual versus group. Similar outcome measures should also be used, both within and between different thalassaemia patient groups. For this purpose, multicentre collaboration, perhaps international, may be needed.

An appropriate review will be possible, if data are reported in the publications describing trials in the future.

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Professor Dame Sally C Davies, Chief Medical Officer and Chief Scientific Advisor, Department of Health, England

Professor Antonio Piga, Thalassaemia Centre, Department of Paediatrics, University of Turin, Italy

Dr Mary Corey, Population Health Sciences, The Hospital for Sick Children, Toronto, Canada

Professor Giuseppe Masera, Department of Paediatrics, University of Milan, Italy

Dr Vanessa Poustie, Institute of Child Health, University of Liverpool, RLCH NHS Trust, UK

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Anie 2001

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Treadwell 2001	Not a randomised controlled trial

APPENDICES

Appendix 1. Search strategies (Embase, Biological Abstracts and CINAHL)

Search strategy

1. thalassaemia or thalassemia
 2. psychology or therapy
 3. explode "psychology"
 4. explode "therapy"
 5. 3 or 4
 6. explode "chelation"
 7. explode "social adjustment"
 8. explode "quality of life"
 9. 1 and 5
 - 10.1 and 6
 - 11.1 and 7
 - 12.1 and 8
-

Appendix 2. Search strategies (PsycLIT and PsycINFO)

Search strategy

1. thalassaemia (search as Keyword) or thalassemia (search as Keyword)
 2. "chelation" (search as Keyword)
 3. explode "social adjustment"
 4. explode "quality of life"
 5. 1 and 2
 6. 1 and 3
 7. 1 and 4
-

Appendix 3. Search strategy (Social Sciences Citation Index)

Search strategy

1. thalassaemia or thalassemia
 2. psychology or therapy
 3. chelation or social adjustment or quality of life
 4. 1 and 2
 5. 1 and 3
-

Appendix 4. Search strategy (Google Scholar)

Search strategy

1. thalassaemia psychology or thalassemia psychology
2. thalassaemia therapy or thalassemia therapy
3. thalassaemia therapy, thalassaemia chelation, thalassaemia social adjustment, thalassaemia quality of life or thalassemia therapy, thalassemia chelation, thalassemia social adjustment, thalassemia quality of life

WHAT'S NEW

Date	Event	Description
13 April 2015	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 3, 2001

Date	Event	Description
14 February 2014	New citation required but conclusions have not changed	A minor update of the review has been completed. No new information or data have been included.
14 February 2014	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register did not identify any potentially eligible trials for inclusion in the review.
24 January 2013	Amended	Contact details updated.
4 November 2011	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any trials potentially eligible for inclusion in the review.
8 September 2010	Amended	Contact details updated.
1 December 2009	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any new references relevant to this review.
15 April 2008	Amended	Converted to new review format.
13 August 2007	Amended	The 'Synopsis' has been replaced by a new 'Plain Language Summary'.
12 August 2007	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any new references eligible for inclusion in the review.
16 August 2006	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any new references eligible for inclusion in the review.

Date	Event	Description
17 August 2005	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register identified no additional trials eligible for inclusion in this review.
19 July 2004	New search has been performed	A search of the Group's trials register identified no additional trials eligible for inclusion in this review.
29 July 2003	New search has been performed	The searches found no new trials eligible for inclusion.
29 July 2003	Amended	The 'Types of outcome measures' have been prioritised into 'Primary' and 'Secondary' outcomes.
7 April 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Both authors discussed the search strategy and key words to be used to identify studies, and the types of interventions.

Dr Kofi Anie then took the lead in the write-up of the review and the update.

Dr Kofi Anie acts as guarantor of the review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

*Psychotherapy; Adaptation, Psychological; Chelation Therapy; Iron Chelating Agents [therapeutic use]; Transfusion Reaction; beta-Thalassemia [psychology] [*therapy]

MeSH check words

Adult; Child; Humans