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Erythrocytapheresis versus phlebotomy for hereditary haemochromatosis (Protocol)

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[Intervention Protocol]

Erythrocytapheresis versus phlebotomy for hereditary haemochromatosis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the benefits and harms of TEA versus phlebotomy in the treatment of hereditary haemochromatosis.

BACKGROUND

Description of the condition

Hereditary haemochromatosis is an autosomal recessive disorder characterised by increased iron absorption and deposition in tissues (Hanson 2001). It is one of the most common inherited disease in Europeans (Bathum 2001), with a prevalence of nearly one in every 300 individuals (Powell 2002).

A mutation in the high iron Fe (HFE) gene (haemochromatosis gene on the short arm of chromosome 6) has been identified to be associated with haemochromatosis (Fairbanks 2001), leading to decreased haepcidin (a down-regulator of iron absorption) production from the liver (Bridle 2003; Fleming 2004), and ensuing dysregulated iron absorption from the intestines (Allen 2008). Two missense mutations have been noted (Feder 1996); the C282Y and H63D. The C282Y is the most common mutation. C282Y homozygotes account for 82% to 90% of clinical diagnoses of hereditary haemochromatosis among persons of northern European descent. It is worth noting that not all those who are homozygous for the C282Y mutation develop clinical features of haemochromatosis, proving the incomplete penetrance of the disease (Olynyk 1999; Adams 2005). Although men and women inherit the disease equally, the higher prevalence among men can be attributed to women's recurrent physiologic blood loss and the slower accumulation of iron (Barton 2005; Allen 2008).

Hereditary haemochromatosis becomes clinically apparent in adults in their forties and fifties (Yen 2006). The toxic accumulation of iron in tissues, particularly the liver, pancreas, heart, joints, and pituitary results in liver cirrhosis, diabetes mellitus, heart failure, arthritis, and impotence. The classic triad of skin pigmentation, cirrhosis, and diabetes mellitus ('bronze diabetes') occurs most commonly in late stages of the disease. Fatigue and abdominal pain are some of the nonspecific, more common symptoms of hereditary haemochromatosis (McDonnel 1999).

Left untreated, hereditary haemochromatosis may result in death from cirrhosis, diabetes, hepatocellular carcinoma, or cardiac disease (Edwards 1998), but early diagnosis and treatment yield a

favourable survival (Waalen 2006).
High plasma transferrin and ferritin levels might suggest iron overload due to hereditary haemochromatosis. Diagnosis is confirmed by genetic testing and liver biopsy. Imaging studies such as magnetic resonance imaging (MRI) might be of potential use in some patients (Adams 2007).

Description of the intervention

Phlebotomy is considered the standard approach to patients with hereditary haemochromatosis. Phlebotomy is used to remove excess iron and maintain low normal body iron stores, and it is recommended to be initiated in men with serum ferritin levels of 300 µg/l or more and in women with serum ferritin levels of 200 µg/l or more, regardless of the presence or absence of symptoms (Barton 1998).
Phlebotomy is suitable treatment for individuals with or without mild anaemia, and whose rate of effective erythropoiesis is sufficient to replace phlebotomy-induced blood losses efficiently (Barton 1998). More than 90% of patients comply with 'induction' phlebotomy to achieve iron depletion, although the proportion of individuals who present for 'maintenance' phlebotomy declines linearly over time (Hicken 2003).
The availability of cell separators has made therapeutic erythrocytapheresis (TEA) a quick and easy procedure for removing red blood cells and hence iron from the circulation. Interest in TEA was raised in haematological centres dealing with thalassaemia or sickle cell disease, and several reports suggested a role for TEA in these patients (Valbonesi 2000). TEA is able to selectively remove red blood cells while sparing plasma proteins, coagulation factors, and platelets. TEA removes more blood erythrocytes per session than phlebotomy (Kellner 1992). TEA is considered safe, well tolerated, and takes less time than phlebotomy to achieve iron depletion (Muncunill 2002).
TEA is considered to reduce iron measures in haemochromatosis patients with severe iron overload, intolerance of phlebotomy, or co-inheritance of beta-thalassaemia (Barton 2007). Combination of recombinant human erythropoietin with TEA have offered better results, even in complicated patients (Kohan 2000; Mariani 2005). Although, TEA costs compared with phlebotomy on the basis of a single session are higher, the total costs for the whole treatment were comparable or cheaper with TEA than with phlebotomy (Rombout-Sestrienkova 2007).

How the intervention might work

The normal iron content of the body is 3 to 4 g, existing as haemoglobin (2.5 g) and as iron-containing proteins (400 mg), iron bound to transferrin in plasma (3 to 7 mg), and ferritin, or haemosiderin in the storage form (Limdi 2004). Serum phlebotomy, TEA, or administration of iron chelating agents (Bring 2008) are the presently known three approaches to remove the excessive iron from the body.
Phlebotomy is considered the standard approach to patients with hereditary haemochromatosis, but this intervention is also known to have its downsides. It is time-consuming and may cause bruises, fatigue, vasovagal reactions, and other adverse effects resulting from bloodletting (Barton 2000; Rombout-Sestrienkova 2007). In addition, phlebotomy cannot be used in patients with severe cardiac disease, anaemia, or hypoproteinaemia. For these patients, iron chelation therapy is considered to be the most effective means for providing iron removal (Rombout-Sestrienkova 2007). Chelation therapy alone seems to be less efficient than phlebotomy and is known for its potentially even more serious local and systemic adverse effects (Kirking 1991; Mariani 2005). The use of serum phlebotomy compared to no intervention and iron chelating agents is studied in another review (Ibrahim 2010). In contrast to phlebotomy, by means of TEA, up to 1000 ml of red blood cells can be removed during a single session, depending on the estimated circulating blood volume. This equals about 800 mg of iron. Therefore, around four times more iron can be removed during a single session of TEA compared with conventional treatment with phlebotomy (Rombout-Sestrienkova 2007).
TEA preserves the valuable blood components of the patient, namely plasma proteins, platelets, clotting factors and leucocytes, which makes this approach also a feasible option for patients with hypoproteinaemia or thrombocytopenia. During a TEA session the patient receives compensation for the removed volume by saline or protein solutions which makes this approach particularly viable for hereditary haemochromatosis patients with severe cardiac disease (Rombout-Sestrienkova 2007).
Assuming a blood volume of 70 ml/kg body weight, the following formula is used to estimate the volume of red blood cells to be removed during the erythrocytapheresis session (VR) VR = [actual haematocrit - desired haematocrit]/79 × 70 ml/kg × body weight (kg) (Rombout-Sestrienkova 2007).

Why it is important to do this review

The opinion that erythrocytapheresis provides a good alternative for the treatment of hereditary haemochromatosis is well established (Rombout-Sestrienkova 2007). However, there are no meta-analyses or systematic reviews to have proven this. In order to find out which of the standard treatment approaches, as mentioned earlier, should be used for patients with hereditary haemochromatosis, we started the conductance of the present review.

OBJECTIVES

To assess the benefits and harms of TEA versus phlebotomy in the treatment of hereditary haemochromatosis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised clinical trials assessing the beneficial and harmful effects of phlebotomy and TEA for hereditary haemochromatosis, irrespective of blinding, publication status, year or language of publication. Regarding harm, we will also include quasi-randomised studies and observational studies.

Types of participants

Patients of all ages, of either sex with evidence of hereditary haemochromatosis through increased iron stores, confirmed by biopsy or genetic testing with or without liver cirrhosis, hepatocellular carcinoma, diabetes mellitus, heart failure, arthropathy, or impotence attributable to iron overload will be included.

Patients will be included irrespective of whether they are treatment-naive or have been previously treated unsuccessfully with any approach known to be used in treating hereditary haemochromatosis.

Patients with or without evidence of concomitant human immunodeficiency virus (HIV) infection, or hepatitis B or hepatitis C infection will be included. Patients with or without prior liver or heart transplantation, or those with concomitant renal failure will also be included.

Types of interventions

Repeated sessions of TEA versus repeated phlebotomy of about 500 ml of whole blood.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Proportion of patients reaching safe blood levels of iron, namely serum ferritin below 50 µg/l and transferrin saturation below 30% (at the end of treatment and maximum post-treatment follow-up).
3. Proportion of patients developing cirrhosis or hepatocellular carcinoma.
4. Adverse events defined as any untoward medical occurrence not necessarily having a causal relationship with the treatment, but resulting in a dose reduction or discontinuation of treatment (ICH-GCP 1997). Severe adverse events are defined as any event that would increase mortality; is life-threatening; requires inpatient hospitalisation; results in a persistent or significant disability; or any important medical event, which may jeopardise the patient or require intervention to prevent it.
5. Quality of life.

Secondary outcomes

1. Proportion of patients without improvement of the specific features of haemochromatosis, namely abdominal pain secondary to hepatomegaly, skin pigmentation, arthralgias, diabetes mellitus, amenorrhoea, loss of libido, impotence, and congestive heart failure.
2. Proportion of patients without improvement of the non-specific clinical features of haemochromatosis, namely weakness, fatigue, lethargy, apathy, and weight loss.
3. Proportion of patients withdrawal from the intervention group due to any reason.
4. Number of sessions needed to reach safe blood iron levels.
5. Cost-effectiveness: the estimated costs connected with the interventions were to be weighed against any possible health gains

Search methods for identification of studies

Electronic searches

We will search *The Cochrane Hepato-Biliary Group Controlled Trials Register* (Gluud 2010), *The Cochrane Central Register of Controlled Trials* (CENTRAL) in *The Cochrane Library*, *MEDLINE*, *EMBASE*, and *Science Citation Index Expanded* (Royle 2003). We have given the preliminary search strategies in Appendix 1 with the expected time span for the searches. As the review progresses, we will improve the search strategies if necessary.

Searching other resources

The bibliographic references of identified randomised clinical trials will be checked in order to find randomised clinical trials not identified by the electronic searches. The principal authors of the identified randomised clinical trials will be approached and inquired about additional randomised clinical trials they might know of.

Data collection and analysis

We will perform the review and meta-analyses following the recommendations of The Cochrane Collaboration (Higgins 2009) and *The Cochrane Hepato-Biliary Group Module* (Gluud 2010). The analyses will be performed using Review Manager 5 (RevMan 2008).

Selection of studies

Two authors will independently identify trials for inclusion. Firstly, titles and abstracts of the records retrieved by the search will be assessed in order to exclude those that are irrelevant. For the remaining records, full-text articles will be retrieved and assessed in order to select trials that meet the inclusion criteria. We will list the trials excluded from the second round and give the reasons for their exclusion.

Data extraction and management

We will develop a template form for data collection and extraction. Data on methods, participants, interventions, and outcomes as listed above, will be extracted. If more than one publication on each randomised clinical trial is identified, data will be extracted from the one providing most pertinent data, eg, longest follow-up. Two authors will extract all the data independently. Disagreements will be resolved by discussion between the two authors. If this does not solve disagreements, a third author will act as an arbiter.

Assessment of risk of bias in included studies

Methodological quality is defined as the confidence that the trial design and report will restrict bias in the intervention comparison (Moher 1998). According to empirical evidence (Schulz 1995; Moher 1998; Jüni 2001; Kjaergard 2001; Wood 2008), bias risk assessment will be achieved through the following domains:

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards and throwing dice are adequate if performed by an independent adjudicator.
- Uncertain risk of bias: the trial is described as randomised, but the method of sequence generation was not specified.
- High risk of bias: the sequence generation method is not, or may not be, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate patients are inadequate and will be excluded for the assessment of benefits but not for harms.

Allocation concealment

- Low risk of bias: allocation was controlled by a central and independent randomisation unit, sequentially numbered, opaque and sealed envelopes or similar, so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
- Uncertain risk of bias: the trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. Quasi-randomised studies will be excluded for the assessment of benefits but not for harms.

Blinding

- Low risk of bias: the trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
- Uncertain risk of bias: the trial was described as blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trial.
- Not performed, the trial was not blinded, so that the allocation was known during the trial.

Incomplete outcome data

- Low risk of bias: the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Uncertain risk of bias: the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- High risk of bias: the number or reasons for dropouts and withdrawals were not described.

Selective outcome reporting

- Low risk of bias: pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
- Uncertain risk of bias: not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Baseline imbalance

- Low risk of bias: if there was baseline balance in important characteristics.
- Uncertain risk of bias: if the baseline characteristics were not reported.
- High risk of bias: if there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation.

Following the evaluation of the above domains, an included trial will be judged as a trial with a low risk of bias if the risk of bias is evaluated as 'low' in all the above domains. If the risk of bias is judged as 'uncertain' or 'high' in just one domain, then the trial will be listed under the group of trials with 'high risk of bias'.

Measures of treatment effect

Dichotomous data

The relative risks with 95% confidence intervals (CI) will be calculated by the fixed-effect model and the random-effects model.

Continuous data

Mean differences with 95% CI will be calculated by the fixed-effect model and the random-effects model.

Unit of analysis issues

In case of cross-over studies, we will follow the guidelines in The Handbook on how to deal with data from cross-over studies (Higgins 2009). We will conduct 'worst-base case scenario' and 'best-worst case scenario' sensitivity analyses.

Dealing with missing data

All analyses will be performed according to the intention-to-treat method, using 'a worst-case scenario' analysis (Gluud 2010) and participants with missing data will be considered as treatment failures.

Assessment of heterogeneity

Statistical heterogeneity will be assessed both by inspection of graphical presentations ('forest plot') (Egger 1997) and calculating the Chi^2 statistic. The statistical heterogeneity is defined significant if $P < 0.1$.

Assessment of bias

Funnel plot asymmetry will be used to assess the existence of publication bias and other biases if there are a minimum number of ten trials (Egger 1997).

Data synthesis

We plan to undertake meta-analyses with fixed-effect model (DeMets 1987) and random-effects model (DerSimonian 1986).

If there is no significant difference between the results, we will present the results, obtained with the fixed-effect model. Otherwise, we will present the results obtained with both models.
In addition, when the overall results are statistically significant by both models, relative risk reduction (RRR), the number-needed-to-treat (NNT), and the number-needed-to-harm (NNH) will also be calculated, if possible.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses according to:

- Risk of bias in the trials.
- Disease severity at entry into the trial, comparing the interventions effects in trials with progressed disease to that in trials with less progressed disease.
- TEA alone versus combination of TEA with recombinant human erythropoietin.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy

Search strategy; searches performed 21 June 2010

Database	Time span of search	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register.	Date will be given at review stage.	(erythrocytapheres* OR cytapheres* OR apheres* OR ((erythrocyte or 'red blood cell*') AND transfusion)) AND (phlebotom* OR venepuncture* OR venipuncture* OR bloodlet*) AND (hemochromatos* OR haemochromatos* OR 'iron overload' OR ironoverload)

(*Continued*)

Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Latest issue.	#1 MeSH descriptor Erythrocyte Transfusionexplode all trees #2 MeSH descriptor Cytapheresisexplode all trees #3 (erythrocytapheres* OR cytapheres* OR apheres* OR ((erythrocyte or 'red blood cell*') AND transfusion)) #4 (#1 OR #2 OR #3) #5 MeSH descriptor Phlebotomy explode all trees #6 phlebotom* OR ven?puncture* OR bloodlet* #7 (#5 OR #6) #8 MeSH descriptor Hemochromatosisexplode all trees #9 h?emochromatos* OR iron overload OR ironoverload #10 (#8 OR #9) #11 (#4 AND #7 AND #10)
MEDLINE(Ovid SP)	1950 to the date of search.	1. exp Erythrocyte Transfusion/ 2. exp Cytapheresis/ 3. (erythrocytapheres* or cytapheres* or apheres* or ((erythrocyte or 'red blood cell*') and transfusion)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 4. 1 or 2 or 3 5. exp Phlebotomy/ 6. (phlebotom* or ven?puncture* or bloodlet*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 7. 5 or 6 8. exp Hemochromatosis/ 9. (h?emochromatos* or iron overload or ironoverload).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 10. 8 or 9 11. 4 and 7 and 10 12. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 13. 11 and 12
EMBASE (Ovid SP)	1980 to the date of search.	1. exp erythrocyte transfusion/ 2. exp cytapheresis/ 3. (erythrocytapheres* or cytapheres* or apheres* or ((erythrocyte or 'red blood cell*') and transfusion)) .mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device man-

(*Continued*)

		ufacturer, drug manufacturer name] 4. 1 or 2 or 3 5. exp phlebotomy/ 6. (phlebotom* or ven?puncture* or bloodlet*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 7. 5 or 6 8. exp hemochromatosis/ 9. (h?emochromatos* or iron overload or ironoverload).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 10. 8 or 9 11. 4 and 7 and 10 12. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 13. 11 and 12
Science Citation Index Expanded (http://apps.isiknowledge.com)	1900 to the date of search.	#1 TS=(erythrocytapheres* OR cytapheres* OR apheres* OR ((erythrocyte or 'red blood cell*') #2 TS=(phlebotom* OR venepuncture* OR venipuncture* OR bloodlet*) #3 TS=(hemochromatos* OR haemochromatos* OR 'iron overload' OR ironoverload) #4 #3 AND #2 AND #1 #5 TS=(random* or blind* or placebo* or meta-analysis) #6 #5 AND #4

WHAT'S NEW

Last assessed as up-to-date: 30 September 2010.

Date	Event	Description
5 November 2010	Amended	DOI number in a reference corrected.

CONTRIBUTIONS OF AUTHORS

All the authors contributed in writing this protocol, and Dr. Nazir Ibrahim checked the final version.

DECLARATIONS OF INTEREST

None