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[Intervention Protocol]

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 evaluate the benefits and harms of phlebotomy for patients with 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). Early diagnosis can be achieved through high degree of suspicion and screening.

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

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patients (Adams 2007)

Description of the intervention

Phlebotomy or bloodletting was first described in1952 by Davis and Arrowsmith, and it is the current standard treatment for patients with haemochromatosis (Davis 1952; Waalen 2006). 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).

Most patients with a clinical phenotype consistent with haemochromatosis (regardless of their genotype) will likely benefit from phlebotomy. Exceptions include patients who have limited life expectancy due to other diseases and those who do not tolerate phlebotomy. The latter patients may instead respond to iron chelation therapy (Barton 1998).

Phlebotomy is suitable treatment for individuals who have no or 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).

Strict dietary restrictions are not demanded in patients undergoing phlebotomy. A normal balanced diet is usually adequate, although reduced intake of iron-containing and iron-fortified foods can prevent excessive dietary iron exposure (Cunningham 2003). Phlebotomy should not be withheld because of advanced age alone or in patients who are asymptomatic (Barton 1998).

How the intervention might work

The aim with the treatment is to remove the excessive iron from the body, which can be accomplished through one of three approaches: serum phlebotomy, therapeutic erythrocytapheresis (TEA), or administration of iron chelating agents (Bring 2008). We will compare phlebotomy to no intervention and chelating agents in this review and we will study TEA in another review (Abolaban 2010).

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).

Some clinical manifestations such as fatigue, malaise, skin pigmentation, insulin requirements in diabetics, and abdominal pain are improved by phlebotomy, but others such as arthropathy and cirrhosis, do not seem to be affected (Tavill 2001).

Despite phlebotomy, hepatocellular carcinoma may continue to be a potential threat, accounting for nearly 30% of deaths from hereditary haemochromatosis (Niederau 1996). The observation that hepatocellular carcinoma is rare in non-cirrhotics substantiates further the rationale for starting phlebotomy prior to the development of cirrhosis (Niederau 1996).

Therapeutic phlebotomy can be carried out in a physician's office, blood bank, or other hospital facility, or at home by a well-trained phlebotomist. Patients should be advised to maintain hydration and avoid vigorous exercise within 24 hours of phlebotomy. Signs of hypovolaemia are more likely in patients with a haemoglobin concentration less than 11 g/dl or a haematocrit less than 33% prior to phlebotomy. These signs include hypotension, tachycardia, increased respiratory rate, dizziness, weakness, and change in mental status and may occur during the phlebotomy or directly after (Barton 1998; Wright 2000; Mariani 2005). Moreover, if the treatment is not properly adjusted, anaemia may result. Therefore, a careful monitoring of each patient throughout treatment is imperative (Barton 2000; Wright 2000).

A once-weekly regimen of venesection of 500 ml of whole blood can be carried out in most patients, and although some patients may tolerate a twice-weekly regimen, this can be rather tedious. A venesection of 500 ml of whole blood eliminates 200 to 250 mg of iron. A weekly schedule of phlebotomy sessions should continue as long as the patient's haematocrit remains 35% or greater before each treatment session. Phlebotomy will need to be continued until safe blood levels of iron are reached, namely serum ferritin below 50 µg/l and transferrin saturation below 30% (Pietrangelo 2007). The lowering of the serum ferritin to 50 µg/l indicates that the body's iron stores have been depleted (Waalen 2006). The length of phlebotomy treatment is subject to the individual patient, but it usually takes one year of weekly phlebotomy to achieve the therapeutic goals. Maintenance phlebotomy typically involves removal of two to four units a year and must be held for life to maintain normal levels of transferrin saturation and serum ferritin (Pietrangelo 2007).

Why it is important to do this review

There is some evidence showing now that starting phlebotomy before the onset of cirrhosis decreases the morbidity and mortality from hereditary haemochromatosis (Niederau 1996). However, there are no systematic reviews or meta-analyses studying phlebotomy for hereditary haemochromatosis.

OBJECTIVES

To evaluate the benefits and harms of phlebotomy for patients with hereditary haemochromatosis.

METHODS

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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 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, hepatitis B infection, 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 phlebotomy (venesection) of about 500 ml of whole blood, two to four times per month, carried out in a physician's office, blood bank, or other hospital facility, or at home by a well-trained phlebotomist versus placebo or no intervention.
- Repeated phlebotomy (venesection) of about 500 ml of whole blood, two to four times per month, carried out in a physician's office, blood bank, or other hospital facility, or at home by a well-trained phlebotomist versus any iron chelating agent.
- One regimen of venesection of whole blood versus a less intensive regimen of venesection 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. 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 try to improve the search strategies.

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.

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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 two of the 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'.

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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).

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. We will conduct 'worst-base case scenario' and 'best-worst case scenario' sensitivity analyses.

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 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 intervention effect of phlebotomy in trials with a progressing disease compared to that in trials with a slowly progressing disease.
- Phlebotomy intervention effect to individual iron chelating agents.
- Phlebotomy regimen, comparing the intervention effect in trials with high intensity phlebotomy to that in trials with less intensity phlebotomy.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search study

Search strategy; searches performed 15 January 2010

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

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(*Continued*)

Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Latest issue at review stage.	#1 MeSH descriptor Phlebotomyexplode all trees #2 phlebotom* OR ven?puncture* OR bloodlet* #3 (#1 OR #2) #4 MeSH descriptor Hemochromatosisexplode all trees #5 h?emochromatos* OR iron overload OR ironoverload #6 (#4 OR #5) #7 (#3 AND #6)
MEDLINE (Ovid SP)	1950 to the date of search.	1. exp Phlebotomy/ 2. (phlebotom* or ven?puncture* or bloodlet*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 3. 1 or 2 4. exp Hemochromatosis/ 5. (h?emochromatos* or iron overload or ironoverload).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 6. 4 or 5 7. 3 and 6 8. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 9. 7 and 8
EMBASE (Ovid SP)	1980 to the date of search.	1. exp phlebotomy/ 2. (phlebotom* or ven?puncture* or bloodlet*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 3. 1 or 2 4. exp hemochromatosis/ 5. (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] 6. 4 or 5 7. 3 and 6 8. (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] 9. 7 and 8

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(*Continued*)

Science Citation Index Expanded (http://apps.isiknowledge.com)	1900 to the date of search.	#5 #4 AND #3 #4 TS=(random* or blind* or placebo* or meta-analysis) #3 #2 AND #1 #2 TS=(h?emochromatos* or iron overload or ironoverload) #1 TS=(phlebotom* or ven?puncture* or blood-let*)

WHAT'S NEW

Last assessed as up-to-date: 4 October 2010.

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

CONTRIBUTIONS OF AUTHORS

Everyone contributed to the draft version of the protocol. N Ibrahim reviewed the final version.

DECLARATIONS OF INTEREST

None

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