Embolisation for pulmonary arteriovenous malformation (Review)

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[Intervention Review]

Embolisation for pulmonary arteriovenous malformation

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Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 8, 2012.
Review content assessed as up-to-date: 6 June 2012.

Citation: Hsu CCT, Kwan GNC, Thompson SA, Evans-Barns H, van Driel ML. Embolisation for pulmonary arteriovenous malformation. *Cochrane Database of Systematic Reviews* 2012, Issue 8. Art. No.: CD008017. DOI: 10.1002/14651858.CD008017.pub3.

ABSTRACT

Background

Pulmonary arteriovenous malformations are abnormal direct connections between the pulmonary artery and pulmonary vein which result in a right-to-left shunt. They are associated with substantial morbidity and mortality mainly from the effects of paradoxical emboli. Potential complications include stroke, cerebral abscess, pulmonary haemorrhage and hypoxaemia. Embolisation is an endovascular intervention based on the occlusion of the feeding arteries the pulmonary arteriovenous malformations thus eliminating the abnormal right-to-left-shunting.

Objectives

To determine the efficacy and safety of embolisation in patients with pulmonary arteriovenous malformations including a comparison with surgical resection and different embolisation devices.

Search methods

We searched the Cystic Fibrosis and Genetic Disorders Group's Trials Register; date of last search: 09 February 2012.

We also searched the following databases: the Australian New Zealand Clinical Trials Registry; ClinicalTrials.gov; International Standard Randomised Controlled Trial Number Register; International Clinical Trials Registry Platform Search Portal (last searched 15 May 2012).

We checked cross-references and searched references from review articles.

Selection criteria

Trials in which individuals with pulmonary arteriovenous malformations were randomly allocated to embolisation compared to no treatment, surgical resection or embolisation using a different embolisation device.

Data collection and analysis

Studies identified for potential inclusion were independently assessed for eligibility by two authors, with excluded studies further checked by a third author. No trials were identified for inclusion in the review and hence no analysis was performed.

Main results

There were no randomised controlled trials identified.

Authors' conclusions

There is no evidence from randomised controlled trials for embolisation of pulmonary arteriovenous malformations. However, randomised controlled trials are not always feasible on ethical grounds. Accumulated data from observational studies suggest that embolisation reduces morbidity. A standardised approach to reporting with long-term follow-up through registry studies can help to strengthen the evidence for embolisation in the absence of randomised controlled trials.

PLAIN LANGUAGE SUMMARY

Embolisation therapy for pulmonary arteriovenous malformations

Pulmonary arteriovenous malformations are abnormal connections between arteries and veins in the lung. They are known to cause serious complications such as stroke, brain abscess, bleeding in the lung and poor oxygenation. Embolisation is the mainstream treatment for pulmonary arteriovenous malformations. During embolisation, balloon or coil embolisation devices, or both combined, are used to block the feeding artery or arteries to the pulmonary arteriovenous malformation. These malformations can often be small, multiple and widely spread out thus not all of them are suitable for embolisation treatment. In this systematic review, we did not identify any randomised controlled trials of embolisation versus surgery or comparing different embolisation devices. While accumulated observational studies have suggested benefits of embolisation, randomised controlled trials are not always feasible on ethical grounds. In the absence of randomised controlled trials, a standardised approach to reporting, as well as long-term follow-up through registry studies can help to improve the safety and outcome of embolisation for pulmonary arteriovenous malformations.

BACKGROUND

Description of the condition

Pulmonary arteriovenous malformations (PAVMs) are abnormal direct connections between a pulmonary artery and a pulmonary vein. The malformations can manifest as a single focal lesion or as multiple lesions. It is estimated that about 90% of individuals with PAVMs have hereditary haemorrhagic telangiectasia (HHT) and only about 50% of individuals with HHT have PAVMs (Cottin 2004; Shovlin 2008a). Therefore, individuals with PAVMs who have not been previously diagnosed with HHT should be tested for the genetic disorder (Shovlin 2008a). The incidence of PAVMs is 1 per 100 000 population with a male to female ratio ranging from 1:1.5 to 1.8 (Abdalla 2006; Khurshid 2002). A large proportion (83%) of PAVMs involves the lower lung zones, with involvement of upper lung zones seen in 17% of individuals (Remy-Jardin 2006). A smaller subset of individuals with PAVMs has a more severe and diffuse pattern of disease which is defined as PAVMs involving every segmental or every subsegmental artery of at least one lobe or most recently re-defined as PAVMs involvement of a single segmental artery rather than a whole lobe (Faughnan 2000; Pierucci 2008). The distribution of diffuse PAVMs are more commonly bilateral (72%) rather than unilateral (28%) (Pierucci 2008); and they are described as being either simple or complex. A simple PAVM is supplied by one artery, whereas the complex variety receives blood supply from two or more arteries. Non HHT-related PAVMs are most commonly sporadic, or secondary to hepato-pulmonary syndrome, caval pulmonary shunts, or trauma (Shovlin 2010).

The approximate prevalence rate of HHT, which is an autosomal dominant disorder, is estimated to be 1 in 50,000 to 80,000 (Dakeishi 2002; Kjeldsen 1999). Individuals with HHT have multiorgan vascular dysplasia, the tendency to form blood vessels without intervening capillaries between an artery and a vein. The connection segment between an artery and a vein tends to be fragile and can rupture and bleed. The affected small blood vessel is termed telangiectasia and the affected larger blood vessel is termed arteriovenous malformation (AVM). Such malformations in HHT are only occasionally congenital; most develop during puberty. In 1999, the Scientific Advisory Board of the HHT Foundation International Incorporated established clinical criteria for the diagnosis of HHT known as the Curaçao criteria (Shovlin 2000). Di-

agnosis of HHT is definite if three criteria are present. A diagnosis of HHT cannot be established in people with only two criteria; however, a high index of clinical suspicion should be maintained. A diagnosis of HHT is unlikely if fewer than two criteria are present. The Curaçao criteria are as follows:

1. epistaxis - spontaneous, recurrent nosebleeds;
2. telangiectases - at characteristic sites (lips, oral cavity, fingers, nose);
3. visceral lesions - such as gastrointestinal telangiectasia (with or without bleeding), pulmonary AVM, hepatic AVM, cerebral AVM, spinal AVM;
4. family history - a first-degree relative with HHT.

Most people with PAVMs are identified as having HHT if it is screened for carefully (Bayrak-Toydemir 2004). A genetically heterogeneous disorder, several subtypes of HHT have been identified including: HHT type 1 associated with *ENG* gene mutation encoding endoglin on chromosome 9 and HHT type 2 associated with *ACVRL1* gene mutation (activin receptor-like kinase1) encoding activin receptor-like kinase (ALK-1) on chromosome 12 (Abdalla 2006). A subset of people with HHT is associated with juvenile polyposis (JPHT) and harbours mutations in the *SMAD4* gene encoding Smad 4 on chromosome 18 (Gallione 2004). There are at least two further unidentified genes that can cause classical HHT mapped to chromosome 5q (HHT type 3) and chromosome 7p (HHT type 4) (Govani 2009). The majority of HHT patients (over 80%) will have mutations in either *ENG* or *ACVRL1* (Gallione 2004).

Description of the intervention

Currently, embolisation is the most commonly used treatment for people with PAVMs. The advantages of embolisation over surgical intervention of PAVMs are that it is less invasive and easy to repeat. The three major indications for treatment include:

1. prevention of neurological complications including stroke and cerebral abscess (Shovlin 2008a);
2. improvement in exercise tolerance (Gupta 2002);
3. prevention of lung haemorrhage.

The radiological literature currently advocates embolisation to be offered to both symptomatic patients and asymptomatic patients with PAVMs of a size amenable to embolisation. In the past, some institutions considered PAVMs of 3 mm as a threshold for embolisation; however, such recommendations were withdrawn in 2006 with suggestions that smaller PAVMs may benefit from embolisation. Treatment of PAVMs less than 3 mm in size has the benefit of protection against bacterial embolisation as well as paradoxic bland embolisation (Pollak 2006). Moreover, smaller PAVMs have the potential to enlarge over time (Pollak 2006; Shovlin 2008a). However, embolisation of smaller vessels is technically difficult because they are harder to cannulate, and this may result in occlusion of larger proximal vessels.

The embolisation procedure is performed by an interventional radiologist. There are variations in practice regarding the use of antibiotic prophylaxis before catheter-directed embolisation, which has the potential to produce bacteraemia (Borrero 2006; Shovlin 2008a). A right femoral venous puncture is used and a catheter is directed into the right and then left pulmonary arteries. The initial angiograms of each side provide a general overview of the number and distribution of PAVMs. During embolisation of PAVMs, the target is the supplying artery immediately preceding the aneurysmal sac. The use of coaxial catheters allows precise placement of the embolisation device and is critical to the outcome of the procedure (White 2007). In the co-axial catheter, the outer or guide catheter, is essential for stable placement while the inner catheter is used for deployment of embolisation device. Once the embolisation device is securely in place, angiography is repeated to determine whether all possible conduits to the aneurysmal sac have been occluded.

How the intervention might work

The choice of embolisation device depends on the vascular anatomy of the individual. In general, PAVMs with feeding artery diameters of 3 to 9 mm are treated with either balloons or coils and those with feeding artery diameters greater than 8 mm are treated with coils alone or with an over-inflated balloon impacted within a nest of coils (Lee 1997; Saluja 1999).

Types of embolisation device:

1. coil (various types of fibered and unfibered, detachable, and pushable coils);
2. detachable balloon;
3. amplatzer vascular plugs, most recent device (Ferro 2007)

The deployed coils are designed to coil within the vessel lumen and carry microfibres which activate platelets to generate an occluding platelet plug, while amplatzer and balloon devices provide direct obstruction to vascular flow. Balloon embolisation offers an additional advantage in that balloon inflation, placement, and location may be adjusted before detachment of the device (Borrero 2006).The most recent embolisation device on the market is the amplatzer vascular plug. This self-expanding cylindrical mesh cage allows a chance of recapture and redeployment until proper positioning is achieved (Ferro 2007). The choice of embolisation device is operator-dependent and correct angiographic assessment of vessel size can prevent device-associated complications such as down-stream migration of the device.

Since embolisation became standard practice in the 1980s, surgical resection of PAVMs has largely been reserved for PAVMs not amenable to embolisation. Surgery is also used as an emergency procedure to control haemorrhage, when loss of lung tissue is justified. Available surgical techniques include different extent of surgical excision of PAVMs: local excision; segmental resection; lobectomy; ligation; and even pneumonectomy, but whenever possible lung conservation resection is the preferred choice of treatment.

It is important to emphasise that the majority of individuals with PAVMs do not have disease suitable for surgery because the size and diffuse distribution of PAVMs. Chest computed tomography (CT) studies indicate that fewer than one third of patients have single PAVMs, and at least 60% to 70% have residual PAVMs too small for embolization (Shovlin 2010). Hence any study comparing surgical resection of PAVMs with embolisation will be feasible only in a small selective portion of people with solitary PAVM and without evidence of PAVMs elsewhere.

Neither embolisation nor surgery will completely eradicate PAVMs in people with HHT, as small PAVMs may persist and new PAVMs may be formed. On the other hand, shunting can be abolished even in people with HHT if large PAVMs are treated. The majority of patients have small shunts. Hence, the use of antibiotic prophylaxis in interventional procedures such as embolisation and dental procedures is still recommended (Borrero 2006; Shovlin 2008a). Embolisation and surgery for PAVMs both require specialised techniques and experience. Procedure complications are operator-dependent and are related to the number of procedures performed annually (Hannan 1989). Since HHT is a multi-organ disease, it is best managed in specialised HHT centres with high-volume experience as well as access to multidisciplinary experts.

Why it is important to do this review

Although the natural history of untreated PAVMs has not been optimally defined, data from observational studies of untreated PAVMs cases demonstrate considerable morbidity including stroke, cerebral abscess, hypoxaemia and haemorrhage (Faughnan 2000; Pollak 2006). Mortality is considered to be caused by PAVMs if death is due to cerebral abscess, stroke, haemoptysis or haemothorax. A study on the prevalence and mortality of HHT in a Danish population found increased mortality, most pronounced amongst those below the age of 60 years, with severe gastrointestinal bleeding and history of untreated PAVMs causing respiratory symptoms as contributor to death (Kjeldsen 1999). A life-expectancy study by Sabbà of 70 people with HHT also showed a decrease in average lifespan of HHT patients compared to a control group, with a reduction of life expectancy approaching 6.8 years. A double peak for mortality was observed with an early peak in the under-50s and a late peak in the 60 to 79 year age group, which can be attributed to major acute complications and chronic organ involvement (Sabbà 2006). The study also highlighted the potential for maternal complications with the deaths of two young women during childbirth, due to haemorrhage from PAVMs and cerebral AVMs (Sabbà 2006). A cohort study by Shovlin provides the first quantification of maternal complications of pregnancy in 111 women with HHT and PAVMs. The study showed that 1.0% of pregnancies resulted in a major pulmonary haemorrhage from the PAVMs; 1.2% in stroke (not all were HHT-related); and 1.0% in maternal death (Shovlin 2008c).

The current practice recommends embolisation of all PAVMs in the absence of contraindications such as severe pulmonary hypertension, renal failure, and early pregnancy. In 2008, a cohort study by Shovlin concluded that it is difficult to predict which HHT patients are at risk of PAVMs complications with reference to PAVMs size, severity and symptoms (Shovlin 2008a). The study suggested the need for greater emphasis on HHT diagnosis, PAVMs screening and the necessity of implementing PAVMs treatment programmes (Shovlin 2008a). This systematic review will provide an overview of the available evidence from the literature and will show the strength of evidence available in order to make recommendations for current practice and future research.

OBJECTIVES

To establish if embolisation is a safe and effective procedure for pulmonary arteriovenous malformations compared to no intervention, as well as a comparison of different embolisation devices. We also planned to include RCTs which compare surgical resection of PAVMs with embolisation. This will be feasible in a small selective portion of patients with single PAVM and without evidence of PAVMs elsewhere.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials.

Types of participants

Participants of all ages with PAVMs with feeding arteries that are determined to be suitable for embolisation. Individuals with both simple and complex PAVMs are included in the review.

Types of interventions

Embolisation techniques compared to no treatment or comparison of two different embolisation devices. Comparisions of embolisation to surgical resection of PAVMs are included as emergency procedures.

Types of outcome measures

Primary outcomes

1. Initial occlusion as determined by angiogram immediately after embolisation
2. Long-term occlusion as determined by
   i) chest radiography (standard posteroanterior and lateral chest radiographs)
   ii) contrast "bubble" echocardiography
   iii) radionuclide shunt study and pulse oximetry (SaO_2)
      a) measured in up-right position
      b) measured in supine position
   iv) computed tomography (CT)
      a) helical CT pulmonary angiogram with 3D reconstruction for assessment of PAVM perfusion (*post hoc* change)
      b) helical CT without contrast media for assessment of PAVM morphology only
3. All causes mortality secondary to PAVM if death was due to any cause, including:
   i) cerebral abscess
   ii) stroke
   iii) haemoptysis
   iv) haemothorax

Secondary outcomes

1. Exercise capacity (comparison with data obtained prior to embolisation)
   i) any recognised and reproducible exercise test e.g. 6-minutes walk test
2. Pulmonary function tests (comparison with data prior to embolisation)
   i) forced expiratory volume in one second (FEV_1)
   ii) vital capacity
   iii) single-breath diffusing capacity for carbon monoxide (D LCO)
   iv) diffusing capacity for carbon monoxide per unit of alveolar volume (KCO[DL/VA]
3. Adverse events
   i) device-related complications (e.g. vascular perforation, intramural arterial dissection, myocardial rupture, device migration, early deflation of balloon, and paradoxical balloon or coil embolisation at the time of deployment)
   ii) procedure-related complications (e.g. pulmonary infarction, pulmonary hypertension, cardiac arrhythmias, thrombophlebitis and deep venous thrombosis and those related to the venous puncture, such as a haematoma, transient symptoms (angina, confusion, bradycardia, and perioral paraesthesias), transient ischaemic attacks and cerebrovascular accident

Search methods for identification of studies

Electronic searches

Using the term 'hereditary haemorrhagic telangiectasia', we searched for relevant trials from the Cystic Fibrosis and Genetic Disorders Group's Trials Registers, compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of *The Cochrane Library*), and quarterly searches of MEDLINE. For details of hand searching, please see the appropriate sections of the Cystic Fibrosis and Genetic Disorders Group's Module.

Latest search of the Group's Trials Register (searched for all years without limitations): 09 February 2012.

The search strategies for *The Cochrane Library* and MEDLINE are presented in the appendices (Appendix 1; Appendix 2). Date of the last search of these databases: 09 February 2012.

We also searched the international registers of clinical trials in the following databases for all years without limitations. Searched terms used "pulmonary arteriovenous malformation(s)" or "PAVM(s)".

- Australian and New Zealand Clinical Trials Registry;
- Clinicaltrials.gov;
- International Standard Randomised Controlled Trial Number Register;
- International Clinical Trials Registry Platform Search Portal.

Latest search date: 15 May 2012.

Searching other resources

In the initial review we contacted medical equipment manufacturers of embolisation devices (Cook Medical and AGA Medical Cooporation, manufacturers of Amplatzer Vascular Plug) and specialised HHT Centers listed by the Osler-Weber-Rendu-HHT Foundation International by email, to identify any unpublished trials. We made no further contacts for the subsequent update of the review in 2012.

We scrutinized references used in the review and identified in the searches for possible published articles.

Data collection and analysis

Since no trials were included in the review, we were unable to carry out any analysis. For future updates, when studies are identified for inclusion in the review, we will apply the following methods.

Selection of studies

Two authors (CC-TH and GNCK) independently assessed studies identified for inclusion in the review using the criteria stated above.

When there were disagreements, the third author (SAT) acted as arbiter.

Data extraction and management

Two authors (CC-TH and GNCK) will independently extract data from the studies included in the review using a standard data extraction form. If there are disagreements, the third author (SAT) will act as arbiter. They will assess outcome measures at time intervals as follows: primary outcomes concerning long-term occlusions, adverse events; and all secondary outcomes measures will be assessed at intervals up to three months, up to six months, up to one year and annually thereafter. If different time points are reported, they will also consider these.

Assessment of risk of bias in included studies

Three authors (CC-TH, GNCK and MLvD) will assess the risk of bias for each study as described in the *Cochrane Handbook for Systematic Reviews of Interventions 5.1* (Higgins 2011) for each of the following domains:

1. randomisation;
2. allocation concealment;
3. blinding (of participants, personnel and outcome assessors);
4. completeness of data;
5. selective outcome reporting;
6. other sources of bias.

Measures of treatment effect

When dealing with dichotomous outcome measures, the authors will calculate a pooled estimate of the treatment effect for each outcome across trials using the odds ratio (OR) (the odds of an outcome among treatment allocated participants to the corresponding odds among controls) and the 95% confidence intervals (CIs). For continuous outcomes, they plan to record either the mean change from baseline for each group or the mean post-intervention values and standard deviations for each group. Then, where appropriate, they plan to calculate a pooled estimate of treatment effect by calculating the mean difference and 95% CIs.

Unit of analysis issues

Cross-over trials are not included in the review because there is only a single treatment designated to each group. If treatment by embolisation is successful, it is inappropriate to expose participants to other forms of intervention, i.e. surgery.

Dealing with missing data

In order to allow an intention-to-treat analysis, the authors plan to seek data on the number of participants with each outcome event by allocated treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from the treatment or follow up. The review authors will request any missing data from the original investigators if appropriate.

Assessment of heterogeneity

The authors plan to assess statistical heterogeneity in the meta-analysis using the I^2 statistic (Higgins 2011) and explore reasons for heterogeneity. Thresholds for the interpretation of I^2 can be misleading, since the importance of inconsistency depends on several factors. The authors plan to use the rough guide to interpretation as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions 5.1* (Higgins 2011).

Assessment of reporting biases

The authors will investigate publication bias using funnel plots if 10 or more studies are identified.

Data synthesis

The authors plan to use a fixed-effect model in their analysis. If they identify heterogeneity (I^2 greater than 50%), they will assess the significance of the treatment effect by using a random-effects model.

Subgroup analysis and investigation of heterogeneity

The authors plan the following subgroup analyses if 10 or more studies are identified, with participants stratified by the following factors:

1. embolisation materials;
    i) coil (various types of fibered and unfibered, detachable, and pushable coils)
    ii) detachable balloon embolisation
    iii) amplatzer vascular plugs
2. emergency treatments of PAVMs - surgical resection versus embolisation;
3. simple versus complex PAVMs;
4. children (up to 18 years) versus adults (18 years and over).

Sensitivity analysis

The authors plan to undertake sensitivity analysis where only trials with adequate allocation concealment and blinding (low risk of bias) are included.

RESULTS

Description of studies

See: Characteristics of excluded studies.

Results of the search

The search of the Cystic Fibrosis and Genetic Disorders Review Group's Trials Registers did not identify any relevant trials. There were also no trials identified from searches of the ongoing trials databases.

The search of *The Cochrane Library* did not identify any trials relevant to the topic. The MEDLINE searches yield did not identify any RCTs, however, nine observational studies relevant to the topic were classified as excluded studies. Cross-referencing failed to identified any RCTs; 17 observational studies relevant to the topic were identified. This includes nine prospective case series listed in Characteristics of excluded studies and 17 retrospective case reviews included in the Additional references.

We contacted the following medical equipment manufacturers of embolisation devices by email, to identify any unpublished trials, but have not yet received a response:

- Cook Medical (contacted 14 November 2009);
- AGA Medical Cooporation, manufacturers of Amplatzer Vascular Plug (contacted 14 November 2009).

We contacted the specialised HHT Centers listed by the Osler-Weber-Rendu-HHT Foundation International by email for results of unpublished clinical studies. Twelve centres responded, with no RCTs identified.

- HHT Center Israel Schneider Children's Medical Center of Israel Rabin Medical Center, Tel Aviv University (replied 14 December 2009): no RCTs identified.
- HHT Center Norway, Rikshospitalet University Hospital (replied 9 December 2009): no RCTs identified.
- The Institute of Vascular Interventional Radiology, The First Affiliated Hospital of China Medical University (replied 8 December 2009): no RCTs identified.
- National HHT Centre Ireland, Mercy University Hospital (replied 6 December 2009): no RCTs identified.
- HHT Center Spain, Hospital Sierrallana (Servicio Cantabro de Salud) (replied 4 December 2009): no RCTs identified.
- HHT Germany-Marburg, Philipps-University (replied 4 December 2009): no RCTs identified.
- HHT Germany-Cologne, Holweide Hospital (replied 2 December 2009): no RCTs identified.
- HHT Germany-Lippspringe, Karl-Hansen Medical Center (replied 2 December 2009): no RCTs identified.
- HHT London, Hammersmith Hospital (replied 27 November 2009): no RCTs identified.
- Edmonton HHT Center (replied 25 November 2009): no RCTs identified.
- Washington University School of Medicine (replied 22 November 2009): no RCTs identified.
- Medical College of Georgia HHT Center (replied 19 November 2009): no RCTs identified

Included studies

No randomised controlled trials have been identified which are eligible for inclusion in the review.

Excluded studies

The studies listed under 'Characteristics of excluded studies' were not eligible for inclusion because they were neither randomised and quasi-randomised controlled trials (Dutton 1995; Gupta 2002; Haitjema 1995; Lacombe 2009; Liu 2010; Pollak 1994; Pollak 2006; Shovlin 2008a; Shovlin 2008b).

Seventeen studies were retrospective case reviews which we did not feel should be listed as 'Excluded studies', but we have listed these in the Additional references section for completeness (Brillet 2007; Cil 2008; Curie 2007; Faughnan 2000; Faughnan 2004; Lee 1997; Mager 2004; Pierucci 2008; Post 2006; Prasad 2004; Remy 1992; Remy-Jardin 2006; Sagara 1998; Saluja 1999; Swanson 1999; White 1983; White 1988).

Risk of bias in included studies

There are no included studies.

Effects of interventions

No eligible studies for inclusion in this review have been identified.

DISCUSSION

Summary of main results

Pulmonary arteriovenous malformation (PAVM) can cause serious neurologic complications (stroke, cerebral abscess), pulmonary haemorrhage and hypoxaemia. The prognosis from historical untreated individuals suggests substantial mortality and morbidity. Overall, approximately 33% of individuals with PAVM will have a history of stroke, 18% of transient ischaemic attack (TIA), 23% of cerebral abscess, 3% of haemothorax and 59% with symptoms of dyspnoea or exercise intolerance (Pollak 2006). A recent publication concluded that HHT cerebral abscesses are strongly associated with PAVM and anaerobic germs and early detection and treatment may avoid recurrence (Mathis 2012).

Embolisation has become mainstream treatment for PAVMs since it was introduced in the 1980s. It is less invasive and may reduce

the risks associated with the original standard surgical treatment. Despite this, we did not find any evidence from RCTs or CCTs assessing the role of embolisation in the management of PAVMs. We excluded 25 observational studies, this number includes nine prospective case series (see Characteristics of excluded studies) and 17 retrospective case reviews (see Additional references).

Agreements and disagreements with other studies or reviews

To date no experimental studies (i.e. RCTs) have supported the fact that embolisation has become mainstream treatment for PAVMs. Information on the effectiveness of the procedure and procedure-related complications is only available from non-controlled, mostly retrospective observational case series.These studies have a high risk of bias, e.g. a biased selection of participants, recall bias due to poor reporting in medical records, and ascertainment bias (Higgins 2011).

A retrospective study by Remy-Jardin evaluated the long-term effectiveness of coil embolisation (38 individuals with 64 PAVMs) over approximately 10 years (Remy-Jardin 2006). Follow-up with CT imaging showed a long-term success rate of 75%; treatment failure was attributed to recanalisation of the occluded feeding artery, previously unrecognised additional feeding arteries of complex PAVMs and development of systemic perfusion of the aneurysmal sac (Remy-Jardin 2006). A prospective study by Pollack using embolisation (415 PAVMs in 155 individuals) emphasised the need for both clinical follow-up and imaging evaluation after embolisation when problems related to PAVMs occurred in 23% of individuals and residual lesions were detected by CT imaging in 2.8% of patients. In addition, CT detected enlargement of previous small PAVMs in 18% of individuals, many of whom were asymptomatic (Pollak 2006).

A prospective study by Shovlin (323 individuals with HHT and PAVMs, median age 45 years) provides the strongest evidence to date showing a significant reduction in the rate of ischaemic stroke following embolisation. However, strokes and brain abscesses occurred in some individuals with small untreatable PAVMs, despite other existing PAVMs having been treated by embolisation (Shovlin 2008a). The benefits of embolisation also extended to those with diffuse pattern of disease with two retrospective reviews suggesting reduction of neurological complications after successful embolisation in most patients (Faughnan 2000; Lacombe 2009). The post-embolisation morbidity and mortality can also be attributed to reperfusion of embolised PAVMs or enlargement of non-embolised PAVMs (Lacombe 2009).

Complications (such as cerebral infarction, chest pain or device-related complications) resulting from embolisation in the excluded observational studies appear to be limited (Lee 1997; Mager 2004; Pollak 2006). A retrospective study showed that embolisation of PAVMs did not lead to a consistent increase in resting pulmonary artery pressure in a series which excluded individuals with severe pulmonary arterial hypertension (Shovlin 2008b). In rare cases, massive haemoptysis has been reported at follow-up post embolisation (Pierucci 2008; Sagara 1998). These can be attributed to the development of bronchial feeding arteries to embolised PAVM.

Evidence suggests that PAVM can occur early in life and present with serious life-threatening complications; however, there are currently only a limited number of observational studies available on embolisation for PAVM in children (Curie 2007; Faughnan 2004). There is only limited evidence from observational studies that children can benefit from embolisation with success and complication rates comparable to adults.

Evidence from observational data only without any comparison to a control group cannot determine if embolisation is the most effective treatment for PAVM. However, given the fact that exposing patients to potentially more harmful procedures (i.e. surgical removal of the PAVM) in a RCT would be undesirable for ethical reasons, it is unlikely that high-level evidence will become available in the near future. In order to strengthen the evidence base for embolisation, a standardised approach to reporting patient characteristics, co-morbidity (and any other potential confounders) and procedures, as well as long-term follow-up protocols are needed.

AUTHORS' CONCLUSIONS

Implications for practice

Embolisation of PAVMs is a minimally invasive procedure which avoids risks associated with general anaesthesia and minimises the loss of pulmonary parenchyma in lung resection surgery. There are no RCTs evidence of embolisation of PAVMs and the current evidence for embolisation is based on retrospective and prospective studies. Results from these observational studies suggest a substantial reduction in mortality and morbidity. The procedure and device complication rates have been minimal, however serious complications include precipitation of pulmonary hypertension and massive haemoptysis. Current recommendations based on observational studies suggest that all PAVMs amenable to embolisation should be treated and that surgery is to be reserved for individuals with PAVMs that are not amenable to embolisation.

Implications for research

It is not always feasible to undertake RCTs on ethical grounds as accumulated evidence from observational studies suggests that embolisation of PAVMs result in substantial reductions in mortality and morbidity. Future RCTs maybe feasible to compare different embolisation devices or techniques. In the absence of RCTs, we suggest a standardised approach to reporting, as well as long-term follow-up through registry studies to help improve the safety and outcome of embolisation for PAVMs.

ACKNOWLEDGEMENTS

We would like to thank Nikki Jahnke, Managing Editor of the Cochrane Cystic Fibrosis and Genetic Disorders Group for her support. We would also like to thank Dr Claire Shovlin for providing an in-depth peer review.

REFERENCES

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Dutton 1995	Prospective case series of 53 participants with PAVMs treated with coil embolisation
Gupta 2002	Prospective case series of 66 consecutive individuals, 225 PAVMs were occluded by coil embolisation
Haitjema 1995	Prospective case series of 32 individuals, 92 PAVMs were treated by coil embolisation
Lacombe 2009	Prospective case series of 39 individuals previously identified to have bilateral PAVMs. 681 PAVMs were occluded by embolisation. 238 PAVMs were treated using the peripheral blood flow redistribution technique
Liu 2010	Prospective study of 23 patients with symptomatic PAVMs underwent endovascular embolization; 7 cases were associated with HHT. During the embolization, microcoils were applied in 6 cases and standard steel coils were used in 17 cases
Pollak 1994	Prospective study of 35 individuals, 96 PAVMs, underwent embolisation with detachable silicone balloon, coil or combination
Pollak 2006	Prospective study of 155 individuals, 415 PAVMs underwent embolisation with balloon, coil or combination of both
Shovlin 2008a	Prospective study of 323 consecutive individuals with PAVMs (n = 219) and/or HHT (n = 305) was performed. Anderson-Gill models assessed constant and time dependent potential predictive variables for stroke/abscess, and rate reduction by PAVMs embolisation
Shovlin 2008b	Prospective study of 143 individuals, 4 individuals were excluded from the study due to severe pulmonary hypertension, underwent embolisation and measurement of pulmonary artery pressure

CT: computed tomography
HHT: hereditary haemorrhagic telangiectasia
PAVMs: pulmonary arterial malformations

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search Strategy for the Cochrane Library (to 09 Feb 2012)

ID	Search
#1	pulmonary near (arteriovenous malformation*)
#2	pulmonary near (arteriovenus fistula)
#3	pulmonary near avm
#4	pulmonary near (a-v malformation)
#5	pavm
#6	(#1 OR #2 OR #3 OR #4 OR #5)

Appendix 2. Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1948 to present (09 Feb 2012) with Daily Update Search Strategy:

#1	exp Arteriovenous Malformations/	21933
#2	arteriovenous malformation$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	13697
#3	arteriovenus fistula.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	2
#4	avm.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	2494
#5	a-v malformation.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	41
#6	4 or 1 or 3 or 2 or 5	23615

(*Continued*)

#7	pulmonary.mp. adj4 (avm.mp. or exp Arteriovenous Malformations/ or arteriovenus fistula.mp. or arteriovenous malformation$.mp. or a-v malformation.mp.) [mp=title, original title, abstract, name of substance word, subject heading word]	2556
#8	PAVM.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	145
#9	8 or 7	2565
#10	exp Embolization, Therapeutic/	20416
#11	emboli#ation.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	29651
#12	11 or 10	31188
#13	9 and 12	530
#14	randomized controlled trial.pt.	280487
#15	controlled clinical trial.pt.	80543
#16	randomized.ab.	189298
#17	placebo.ab.	115470
#18	drug therapy.fs.	1347511
#19	randomly.ab.	137122
#20	trial.ab.	196159
#21	groups.ab.	936463
#22	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	2468635
#23	(animals not (humans and animals)).sh.	3350294
#24	22 not 23	2092778
#25	24 and 13	21
#26	from 25 keep 1-21	21

WHAT'S NEW

Last assessed as up-to-date: 6 June 2012.

Date	Event	Description
6 June 2012	New citation required but conclusions have not changed	As no new studies have been included, the conclusions of this review have not changed
6 June 2012	New search has been performed	A search of the CFGD Group's registers and MEDLINE did not identify any new references which were potentially eligible for inclusion in this review. One additional reference was added to the list of excluded studies (Liu 2010).

HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 5, 2010

CONTRIBUTIONS OF AUTHORS

The original review was written by Charlie Chia-Tsong Hsu (CC-TH) and Gigi Nga Chi Kwan (GNCK) with comments from Shane Anthony Thompson (SAT). Mieke L van Driel (MLvD) provided support with the methodological aspects of the review. All authors contributed to drafting the protocol and the review and agreed on the final version.

At the first update of the review (2012), Hannah Evans-Barnes joined the review team. All authors contributed to updating the review and agreed on the final version.

DECLARATIONS OF INTEREST

None Known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Following peer review comments at draft review stage it was decided to extend the scope of the review to include a comparison of different embolisation devices.

Helical computer tomography (CT) pulmonary angiogram and helical CT without contrast media with three-dimensional reconstruction is a reliable tool for assessment of PAVMs prior to embolization and in the follow-up period. These outcome measures included in the outcome measure in the 2012 updated review (Remy 1994; Remy-Jardin 2006).

INDEX TERMS

Medical Subject Headings (MeSH)

Arteriovenous Malformations [*therapy]; Embolization, Therapeutic [adverse effects; *methods]; Pulmonary Artery [*abnormalities]; Pulmonary Veins [*abnormalities]

MeSH check words

Humans