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ORIGINAL ARTICLE

Medical Therapy and Balloon Angioplasty for Inoperable Chronic Thromboembolic Pulmonary Hypertension: A Systematic Review and Meta-analysis

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Q5 **Background** A significant number of chronic thromboembolic pulmonary hypertension (CTEPH) patients will have an inoperable disease. Medical therapy and balloon pulmonary angioplasty (BPA) have provided alternate therapeutic options for patients with inoperable CTEPH, although there are a limited number of published studies examining the outcomes. Thus, our study aims to evaluate and compare the efficacy of medical therapy and BPA in patients with inoperable CTEPH.

Q6 **Methods** An electronic search of six databases was performed and the search results were screened against established criteria for inclusion into this study. Data was extracted and meta-analytical techniques were used to analyse the data.

Results Pooled data from RCTs revealed that medical therapy, compared with a placebo, was associated with a significant improvement of at least one functional class ($P = 0.038$). With regards to pulmonary haemodynamics, medical therapy also resulted in a significant reduction in both mean pulmonary arterial pressure (mPAP) ($P = 0.002$) and pulmonary vascular resistance (PVR) ($P < 0.001$). From the included observational studies, the 6-minute walk distance (6MWD) significantly increased following medical therapy by an average of 22.8% ($P < 0.001$). The pooled improvement in 6MWD was found to be significantly higher in the BPA group when compared to medical therapy for CTEPH ($P = 0.001$). Pooled data from available observational studies of medical therapy or BPA all demonstrated significant improvements in mPAP and PVR for pre versus post intervention comparisons. The improvement in mPAP ($P = 0.002$) and PVR ($P = 0.002$) were significantly greater for BPA intervention when compared to medical therapy.

Conclusions High-quality evidence supports the use of targeted medical therapy in improving haemodynamics in patients with inoperable CTEPH. There is only moderate-quality evidence from observational studies supporting the efficacy of BPA in improving both haemodynamics and exercise capacity. Further RCTs and prospective observational studies comparing medical therapy and BPA in patients with inoperable CTEPH are required.

Keywords Hypertension • Balloon pulmonary angioplasty: Medical therapy • Haemodynamics • Inoperable • Systematic review • Meta analysis

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Introduction

Q7 Chronic thromboembolic pulmonary hypertension (CTEPH) develops in 1–4% of patients following an acute episode of pulmonary embolism [1–4]. It is an under-diagnosed but severe condition due to chronic organisation of non-resolving thrombi within the pulmonary arteries, resulting in an elevation of pulmonary artery pressure and, ultimately, right heart failure, if left untreated [5–7]. CTEPH is haemodynamically defined by the presence of precapillary pulmonary hypertension (mean pulmonary artery pressure ≥25 mmHg and pulmonary artery wedge pressure ≤15 mmHg), together with the demonstration of obstructive lesions within the pulmonary arteries on imaging despite three months of anti-
Q8 coagulation [7,8].

Pulmonary endarterectomy (PEA) is the preferred management strategy for patients with CTEPH who have disease amenable for surgery following assessment by a multidisciplinary CTEPH team [7,8]. Although PEA is potentially curative and should be offered as first-line therapy for CTEPH [9], a significant number of CTEPH patients will have an inoperable disease, for reasons such as the predominance of distal lesions that are technically inaccessible by the surgeon, or the presence of severe medical co-morbidities that preclude surgery. In experienced CTEPH centres, up to 30–40% of patients are deemed to have an inoperable disease following multidisciplinary team evaluation [10,11]. In addition, 15–30% of patients will have persistent or recurrent pulmonary hypertension following PEA [12–14]. Thus, there is an unmet need for efficacious therapies for patients with inoperable CTEPH.

A large number of efficacious agents targeting the prostacyclin, endothelin-1 and nitric oxide pathways are now approved for the treatment of pulmonary arterial hypertension (PAH) [15]. Due to similarities in the distal vasculopathy found in PAH and inoperable CTEPH, the use of targeted medical therapy has been explored for inoperable CTEPH. In clinical practice, ''off-label'' targeted medical therapies are used frequently despite the inconsistent data from both randomised and observational studies [16].

More recently, the novel technique of balloon pulmonary angioplasty (BPA) has provided a new therapeutic option for patients with inoperable CTEPH [17,18]. Technical refinements of this technique have improved both its safety and efficacy, and current pulmonary hypertension guidelines have incorporated BPA in the management algorithm of inoperable CTEPH, despite the limited number of published studies [19].

The main aim of our study was to evaluate the available evidence of medical therapy and BPA in patients with inoperable CTEPH by performing a systematic review and meta-analysis of the available literature. An additional aim of our study was to compare the efficacy of medical therapy against BPA in patients with inoperable CTEPH.

Materials and Methods

The present systematic review and meta-analysis was conducted according to the international Prevention and Recovery Information System for Monitoring and Analysis (PRISMA) guidelines [20].

Literature Search

Electronic searches were performed using Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club and Database of Abstracts of Review of Effectiveness (DARE) from their dates of inception to August 2015. To achieve maximum sensitivity of the search strategy and identify all studies, we searched the terms: ''chronic thromboembolic pulmonary hypertension'', ''chronic pulmonary embolism'', ''chronic thromboembolic disease'' as either keywords or MeSH terms. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. All identified articles were systematically assessed using the inclusion and exclusion criteria.

Selection Criteria

Eligible randomised controlled studies for the present study included those which compared medical therapy against placebo for inoperable CTEPH. Medical therapy included drugs included the following classes of drugs: prostanoids, endothelin-1 receptor antagonists, phosphodiesterase type-5 inhibitors and soluble guanylate cyclase stimulators. Due to the very small number of RCTs of medical therapy in inoperable CTEPH and the absence of any randomised-controlled data for BPA, we also included eligible observation studies which report efficacy and safety outcomes for both medical therapy and BPA for the present systematic review and meta-analysis. For observational studies, at least 10 subjects were required for inclusion. Studies that did not include at least one of the following end-points were excluded: 6-minute walk test (6MWT), functional class (FC), mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR). When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for quantitative assessment at each time interval. All publications were limited to those involving human subjects and in the English language. Abstracts, case reports, conference presentations, editorials and expert opinions were excluded. Review articles were omitted because of potential publication bias and duplication of results.

Data Extraction and Critical Appraisal

All data were extracted from article texts, tables and figures. Two investigators independently reviewed each retrieved article (EL and HJ). Discrepancies between the two reviewers were resolved by discussion and consensus. Assessment of risk of bias for each selected study was performed according to the most recently updated Cochrane statement. Discrepancies between the two reviewers were resolved by

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