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Systematic Review/Meta-analysis

The Medical Treatment of New-Onset Peripartum Cardiomyopathy: A Systematic Review of Prospective Studies

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See editorial by Cardona-Guarache and Kron, pages 1418–1420 of this issue.

ABSTRACT

Background: Peripartum cardiomyopathy (PPCM) is a rare disorder with potentially fatal consequences, which occurs mainly in previously healthy women. The aetiology of PPCM remains unknown and various pathologic mechanisms have been proposed, including immune-mediated injuries and impaired response to oxidative stress and inflammatory cytokines. Several therapies have been studied, but few have been validated in a well-designed randomized controlled trial.

Methods: In the present study we sought to review the medical treatment intended for acute PPCM. To this end, we performed a systematic review of the literature of randomized and nonrandomized prospective clinical studies.

Results: We identified 2 randomized controlled trials that evaluated the dopamine agonist bromocriptine and the inotrope levosimendan, respectively, and 1 nonrandomized study that evaluated the nonselective phosphodiesterase inhibitor pentoxifylline. We reviewed the

RÉSUMÉ

Introduction : La cardiomyopathie du péripartum (CMPP) qui est un trouble rare dont les conséquences sont potentiellement fatales apparaît principalement chez des femmes auparavant en bonne santé. On ignore l'étiologie de la CMPP, mais de nombreux mécanismes pathologiques ont été proposés, dont les lésions à médiation immunitaire et la détérioration de la réponse au stress oxydatif, ainsi que les cytokines inflammatoires. Plusieurs traitements ont été étudiés, mais peu ont été validés au cours d'un essai clinique à répartition aléatoire bien conçu.

Méthodes : Dans la présente étude, nous avons cherché à passer en revue le traitement médical prévu contre la CMPP aiguë. À cette fin, nous avons réalisé une revue systématique des études cliniques prospectives à répartition aléatoire et non aléatoire.

Résultats : Nous avons trouvé 2 études cliniques à répartition aléatoire qui évaluaient respectivement l'agoniste dopaminergique, la

Peripartum cardiomyopathy (PPCM) is a rare disorder with potentially fatal consequences.[1-3] It presents as a heart failure syndrome with a left ventricular ejection fraction < 45% within 1 month before delivery to 5 months postpartum.[4] The exact aetiology of PPCM remains unknown and various pathologic mechanisms have been proposed, including immune-mediated injuries, viral infections, and impaired response to oxidative stress and inflammatory cytokines.[5-7]

The incidence of PPCM varies greatly by region. There are no Canadian data available to date, but the incidence in the United States ranges from 3.6 to 4.8 cases per 10,000 live births.[1,8,9] Between 2000 and 2009 in Scotland, the incidence was estimated to be 1 for 6878 live births. African-American women seem to have the highest incidence of PPCM with a 16-fold increased risk compared with non-African-American women.[10] Other risk factors associated with the development of PPCM include multiparity, older maternal age, multifetal pregnancy, pre-eclampsia, gestational hypertension, and prolonged tocolysis.[11,12]

Clinical findings are most in keeping with other types of acutely decompensated cardiomyopathies. Symptoms include orthopnea, paroxysmal nocturnal dyspnea, pedal edema, chest pain, shortness of breath at rest and/or on exertion,

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pathophysiological, pharmacological, and clinical properties for each treatment option identified. Bromocriptine and pentoxifylline both improved left ventricular systolic function and patient-oriented clinical end points and levosimendan did not improve mortality or echocardiographic findings of PPCM.

Conclusions: In this review we identified bromocriptine and pentoxifylline, but not levosimendan, as potentially useful agents to improve left ventricle function and outcomes in PPCM.

bromocriptine, et l'agent inotrope, le lévosimendan, et 1 étude à répartition non aléatoire qui évaluait l'inhibiteur non sélectif des phosphodiestérases, la pentoxifylline. Nous avons passé en revue les propriétés physiopathologiques, pharmacologiques et cliniques de chacune des options de traitement établies. La bromocriptine et la pentoxifylline ont amélioré la fonction systolique du ventricule gauche et les critères cliniques axés sur le patient, et le lévosimendan n'a pas amélioré la mortalité ou les résultats échocardiographiques de la CMPP.

Conclusions : Dans cette revue, nous avons établi que la bromocriptine et la pentoxifylline, mais non le lévosimendan, sont des agents potentiellement utiles à l'amélioration de la fonction du ventricule gauche et des résultats de la CMPP.

palpitations, and cough.[13,14] Albeit difficult to discern from physiologic pregnancy changes, there can also be symptoms of abdominal distension and discomfort. Most patients present with grade III/IV New York Heart Association (NYHA) functional class. In one study, a displaced apical impulse, an S_3 and mitral regurgitation were the most common physical findings in patients with PPCM.[8,14]

Despite current advances in heart failure treatment, mortality related to PPCM at 1 and 10 years can be as high as 4% and 7%, respectively.[15] Strikingly, these young, otherwise healthy women tend to die from sudden cardiac death or progressive heart failure with 18% of deaths occurring by the first week and 87% by the sixth month after their diagnosis is made. For every 10 women with fulminant-onset PPCM, 1 will require heart transplantation.[16]

To date, no specific tailored treatment is recommended for PPCM, apart from guideline-based therapy for heart failure.[8] A recent study revealed that women with decreased left ventricular ejection fraction (LVEF) at the time of diagnosis were at higher risk of adverse cardiac events (such as overall mortality, cardiac transplantation, need for circulatory support, cardiac arrest, pulmonary edema, thromboembolic events, and defibrillator or pacemaker implantation).[17] These data are concerning and warrant the need for disease-targeted therapies to increase LVEF and improve outcomes. Several pharmacological agents meant to target the pathologic mechanisms of PPCM have been proposed, but few have been tested in clinical trials.

In the present work we sought to review the medical literature on therapies specifically intended for acute-onset PPCM. To this end, we performed a systematic review and herein discuss the pathophysiological, pharmacological, and clinical properties for each treatment option identified.

Methods

A systematic review of prospective clinical studies that focused on the treatment of PPCM was performed. Screened databases were Medline, EMBASE, and Cochrane Central Register of Controlled Trials through October 18, 2014 (Supplemental Table S1). The literature search included all treatment strategies studied for the treatment of PPCM.

For the primary search, 2 authors (M.T.-G. and G.M.-G.) independently screened the titles and abstracts to select potentially relevant articles. Selected articles underwent full evaluation to assess their potential inclusion in the systematic review. A third reviewer resolved disagreements (R.A.). The systematic literature search was completed with a review of the abstracts from the major cardiovascular conferences (American Heart Association, American College of Cardiology, European Society of Cardiology, and Canadian Cardiovascular Society) from 2008 to 2013 by a fourth collaborator (O.D.), and by manual search of the retrieved articles. Through October 13, 2014, the clinicaltrials.gov database was surveyed for relevant ongoing studies, and authors were contacted when possible. A manual search of abstracts from the American Heart Association Scientific Sessions, American College of Cardiology Scientific Sessions, and the European Society of Cardiology Congress from 2010 to 2014 years was also performed.

Results

The results of the search are summarized in Figure 1. Two randomized controlled trials that evaluated bromocriptine[18] and levosimendan,[19] and 1 nonrandomized study that evaluated pentoxifylline[20] were identified. The quality of reporting for the selected reports is presented in Supplemental Table S2. A summary of the systematic review results is presented in Table 1.

Bromocriptine

Serum levels of a fragment of prolactin, called 16kDa prolactin, increase during the puerperal period. In women who develop PPCM, the 16kDa prolactin fragment is overexpressed and is thought to initiate and perpetrate excessive oxidative stress through reactive oxygen species, which then induces apoptosis via ischemia-reperfusion and hypoxia-reoxygenation mechanisms. This culminates in myocardial dysfunction and symptomatic heart failure.[21-25] Dopaminergic inhibition of prolactin secretion achieved with bromocriptine, sometimes referred to as lactation suppression, is thought to thwart prolactin's deleterious effects on cardiac function.[26]

Early reports of severe cardiovascular adverse events including stroke,[27] thrombotic,[28] and vasospastic[29-31] infarctions associated with bromocriptine led to concerns regarding its use in postpartum women for milk suppression. In 1995, the United States Food and Drug Administration withdrew its indication in the postpartum period because of these adverse events.[32] However, the exact mechanisms underlying these adverse effects are mainly speculative and