Pentoxifylline for heart failure: a systematic review

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Background. Recent trials have indicated a beneficial effect of pentoxifylline on measures of inflammation and markers of cardiac dysfunction in people with heart failure. However, it is uncertain whether pentoxifylline should be used routinely in the management of heart failure.

Objective. To determine the effectiveness of pentoxifylline in heart failure.

Design. Systematic review of randomised controlled trials.

Methods. We searched MEDLINE (1 January 1966 - 20 November 2004), the Cochrane Controlled Trials Register (issue 4, 2004), and reference lists of related papers, for randomised controlled trials of pentoxifylline in the treatment of heart failure. Prospective, randomised, double-blind controlled trials were sought for inclusion in the study. The two reviewers independently assessed trial quality and extracted data, which were analysed using RevMan statistical software. The following outcome measures were evaluated: (*i*) New York Heart Association (NYHA) functional class; (*ii*) left ventricular ejection fraction (LVEF); (*iii*) frequency of hospitalisation; and (*iv*) death from all causes.

Results. Four studies with a total of 144 participants met the inclusion criteria. Statistical pooling (or meta-analysis) was not performed owing to the significant clinical heterogeneity and differences in reporting of the outcomes in the included studies; instead, the trials were analysed separately for the outcomes of interest. The four studies tested the use of pentoxifylline versus placebo in patients with heart failure of varying aetiology (idiopathic dilated cardiomyopathy, 3 studies; ischaemic cardiomyopathy, 1 study). In 2 of the idiopathic dilated cardiomyopathy studies, patients were classified as NYHA class II or III, while the study population in another idiopathic cardiomyopathy study was in NYHA class IV. The trial of patients with ischaemic cardiomyopathy included patients in NYHA functional classes I - IV. The use of pentoxifylline was associated with significant improvement in symptoms (i.e. NYHA functional class) and cardiac function (i.e. LVEF) in 3 out of 4 studies. The beneficial effect on symptoms of heart failure and cardiac function was seen in all grades of severity of heart failure and in patients with ischaemic and idiopathic dilated cardiomyopathy. All 4 studies showed a trend towards reduction of mortality, but this effect was not statistically significant. The effect of pentoxifylline on the frequency of hospitalisation has not been tested in randomised controlled trials.

Interpretation. Pentoxifylline may have a beneficial effect on NYHA functional class, ejection fraction and mortality in heart failure, but published trials are too small to provide conclusive evidence. There is a need for large, placebo-controlled trials of pentoxifylline in heart failure, involving a diverse group of patients with regard to cause and severity of heart failure.

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Heart failure, typically a progressive disease, now affects 22 million people worldwide.[1] Over the past 50 years great strides have been made in developing treatments for end-stage heart failure, but these measures remain largely palliative.[2] The diagnosis of heart failure is associated with a poor prognosis, with only 35% of patients surviving 5 years after the first diagnosis.[3] For patients with the most advanced phase of heart failure, heart transplantation has been the only means of improving quality of life and survival, but this option is available to only a fraction of those needing it because of the shortage of donors.[2] There is therefore a need to identify new and more effective treatments for heart failure.

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Recent research findings have suggested that pentoxifylline may have beneficial effects when added to the standard treatment for heart failure.[4-9] Pentoxifylline, a purine derivative, is a peripheral vasodilator agent that is thought to work by improving the flow properties of blood; it improves erythrocyte flexibility, reduces platelet aggregation, reduces blood viscosity and improves microcirculatory blood flow. Pentoxifylline is also an inhibitor of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), and it inhibits apoptosis in different human cell types *in vitro* and *in vivo*; high plasma TNF-α levels and increased apoptosis of cardiac cells may contribute to disease progression and mortality in heart failure.[10,11] The vasodilatory, anti-inflammatory and anti-apoptotic properties of pentoxifylline have made it a prime candidate for the treatment of heart failure.

We conducted a systematic review of the world literature to determine whether the addition of pentoxifylline to standard

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treatment leads to improvement in symptoms, cardiac function, frequency of hospitalisation and death rate in people with heart failure.

Methods

We considered randomised placebo-controlled trials comparing the use of pentoxifylline with placebo in patients of all ages with a clinical diagnosis of heart failure. We examined the effect of pentoxifylline on the following outcome measures: (i) New York Heart Association (NYHA) functional class; (ii) left ventricular ejection fraction (LVEF); (iii) frequency of hospitalisation; and (iv) death from all causes.

Studies selected for review were identified from the following sources: (i) MEDLINE (1 January 1966 - 20 November 2004); (ii) the Cochrane Controlled Trials Register (issue 4, 2004); and (iii) reference lists of existing studies of pentoxifylline in the treatment of heart failure.

Two reviewers (KB and BMM) independently searched the literature and identified possible trials for review; we were looking for prospective double-blind randomised controlled trials. Studies that were not randomised controlled trials were excluded. Information from each study was entered into a data extraction form that included details of the authors, duration of the study, nature of allocation concealment and double blinding, and outcomes of each trial. Data were analysed using the RevMan (version 4.1) statistical software for derivation of the following statistical estimates of effect: odds ratios (ORs) for dichotomous outcomes or weighted mean differences (WMDs) for continuous outcomes, 95% confidence intervals (CIs) and p-values.[12]

A 5-point quality scale was used to assess the methodological quality of the included studies (Table I). The 5-point quality scale included the generation of the allocation sequence (2 points — computer-generated random numbers or similar; 1 point — not described; 0 point — quasi-randomised trial); double-blinding (2 points — identical placebo tablets or similar; 1 point — not described; 0 point — no blinding or inadequate method, such as tablets versus injections or similar); and follow-up (1 point — number and reasons for dropouts and withdrawals described; 0 point, number and/or reasons for dropouts and withdrawals not described). The quality score was ranked as low (≤ 2 points) or high (≥ 3 points).[13]

The included studies were analysed separately and not combined in a meta-analysis, as initially planned, for the following reasons: (i) considerable clinical heterogeneity existed among selected trials, for example patients differed from trial to trial with regard to cause of heart failure (e.g. peripartum cardiomyopathy versus idiopathic dilated cardiomyopathy), severity of symptoms as assessed by NYHA

functional class, and available treatments (e.g. pre-β-blocker versus β-blocker era); and (ii) trials reported data in different forms (e.g. the trials by Sliwa et al. (1998),[4] Skudicky et al. (2000),[5] and Skudicky et al. (2001)[6] reported data in a dichotomous form, while data in the trials by Sliwa et al. (2002)[7] and Sliwa et al. (2004)[8] were reported as continuous measures), making meta-analysis difficult without access to the individual participant data.

Results

Description of studies

Four studies with a sample size varying from 18 to 49 and a total of 144 participants met the inclusion criteria.[4-7,9] According to the published reports, the study by Skudicky et al.[5] (2000) was an extension study of the trial by Sliwa et al.[4] (1998), thus the 2 trials were reviewed as 1 to avoid double counting of the study participants. Details of studies included in this systematic review are given in Table I. All trials involved patients of black African descent and the same group of investigators in Johannesburg, South Africa. Patients in 2 of the studies were classified as either NYHA functional class II or III.[4-6] In 1 of the studies, they were classified as functional class IV,[7] and in the other study patients from all functional class groupings were included.[9] Patients in 3 of the trials were diagnosed with idiopathic dilated cardiomyopathy,[4-7] while those in the fourth study had ischaemic cardiomyopathy.[9] All patients exhibited LVEFs of ≤ 40%. The length of follow-up was 6 months in all studies[4-6,9] except 1.[7] The outcomes measured in the trials are indicated in Table I. None of the trials reported on the frequency of hospitalisation as an outcome measure.

Methodological quality of included studies

The studies included in this systematic review were generally of good methodological quality (Table I), but there was variation in reporting the method of randomisation and concealment of allocation sequence. In 2 studies, the randomisation list was computer-generated by the Statistics Department at the University of the Witwatersrand, with an equal number assigned to receive pentoxifylline and placebo.[4,5,9] The remaining 2 trials did not specify randomisation techniques.[6,7] The selected trials were reported to be double-blind studies, but the method of allocation concealment was not given in any of the studies. The Skudicky et al.[6] (2001) trial specified loss to follow-up and utilised intention-to-treat analysis. Loss to follow-up was specified in the Sliwa et al.[4] (1998) trial, but intention-to-treat analysis was not employed. Loss to follow-up was not reported in the remaining trials, nor were there references to intention-to-treat analyses.

Table I. Studies included in this review

Study	Patients	N	Interventions	Outcomes	Study grading (5-point quality grading scale)*
Sliwa et al.[4] (1998)	Patients with idiopathic dilated cardiomyopathy and congestive heart failure classified as NYHA functional class II or III, with a LVEF of ≤ 40%, aged 18 - 70 years and in sinus rhythm	28	Intervention: pentoxifylline 400 mg TID for 6 months (in addition to digoxin, ACE inhibitors and diuretics, initiated at least 4 months before randomisation) Control: matching placebo and conventional therapy (of digoxin, ACE inhibitors and diuretics, initiated at least 4 months before randomisation) for 6 months	NYHA functional class; left ventricular function (systolic and diastolic); left ventricular dimensions; LVEF	2 + 2 + 1 = 5 high-quality score
Skudicky et al.[5] (2000)	Patients with idiopathic dilated cardiomyopathy in NYHA functional class II or III with a LVEF of ≤ 40%	49	Intervention: pentoxifylline 400 mg TID for 6 months (in addition to conventional therapy of digoxin, ACE inhibitors and diuretics) Control: matching placebo and conventional therapy (of digoxin, ACE inhibitors and diuretics)	LVEF; TNF-alpha and Fas/APO-1 plasma concentrations; left ventricular diameter	2 + 2 + 1 = 5 high-quality score
Skudicky et al.[6] (2001)	Patients with idiopathic dilated cardiomyopathy in NYHA functional class II or III with a LVEF of < 40%, aged 18 - 70 years and in sinus rhythm	39	Intervention: pentoxifylline 400 mg TID for 6 months (in addition to digoxin, ACE inhibitors and carvedilol, initiated 3 months before randomisation) Control: matching placebo (in addition to digoxin, ACE inhibitors and carvedilol, initiated 3 months prior to randomisation)	NYHA functional class; left ventricular function (systolic and diastolic); left ventricular size; exercise tolerance	1 + 2 + 0 = 3 high-quality score
Sliwa et al.[7] (2002)	Patients with idiopathic dilated cardiomyopathy aged ″ 18 years with NYHA class IV heart failure, a LVEF ″ 40%, a left ventricular end diastolic diameter of > 55 mm, and in sinus rhythm	18	All patients received intravenous dobutamine for at least the first 72 hours of the study Intervention: pentoxifylline 400 mg TID for 1 month (in addition to conventional therapy of diuretics, digoxin and ACE inhibitors) Control: matching placebo and conventional therapy (of diuretics, digoxin and ACE inhibitors).	NYHA functional class; LVEF; left ventricular dimensions; plasma cytokine and Fas/APO-1 levels; haemodynamics	1 + 2 + 0 = 3 high-quality score
Sliwa et al.[9] (2004)	Patients with ischaemic cardiomyopathy, aged 18 - 70 years with NYHA class I - IV heart failure, a LVEF ″ 40%, and in sinus rhythm	38	All patients received optimal medical therapy for 3 months before randomisation Intervention: pentoxifylline 400 mg TID for 6 months (in addition to ACE inhibitors, β-blockers, diuretics and spironolactone) Control: matching placebo (in addition to ACE inhibitors, β-blockers, diuretics and spironolactone)	LVEF; NYHA functional class; clinical assessment; plasma TNF-α, Fas/APO-1, high-sensitivity C-reactive protein and NT-pro BNP levels; left ventricular dimensions	2 + 2 + 0 = 4 high-quality score

N = number of participants in a trial; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; TID = three times daily; ACE = angiotensin-converting enzyme;
* See methods section for an explanation of the trial grading method.

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Main findings

Improvement in NYHA functional class

In the Sliwa et al.[4] (1998) trial comparing the use of pentoxifylline and placebo in 28 idiopathic dilated cardiomyopathy patients in NYHA class II - III heart failure, pentoxifylline was associated with an improvement in NYHA functional class. However, this effect was not statistically significant (OR 3.33, 95% CI: 0.69 - 16.02, $p = 0.13$). However, a statistically significant improvement in NYHA functional class was found with the use of pentoxifylline when the number of patients was increased to 39 in this study (OR 15.79, 95% CI 2.80 - 89.00, $p = 0.02$).[5] A similar result was found in 18 patients with idiopathic dilated cardiomyopathy in NYHA class IV heart failure (WMD 1.00, 95% CI: 0.26 - 1.74, $p = 0.009$).[7] These findings in patients with idiopathic dilated cardiomyopathy were subsequently extended to patients with heart failure due to ischaemic cardiomyopathy; 38 such patients in NYHA class I - IV heart failure had statistically significant improvement in effort tolerance following the addition of pentoxifylline (WMD –0.90, 95% CI: –1.35 - 0.45, $p = 0.00009$).[9]

Improvement in ejection fraction

In patients with heart failure due to idiopathic and ischaemic cardiomyopathy, pentoxifylline use was associated with an improvement in LVEF. In the Skudicky et al.[5] (2000) trial of patients with idiopathic dilated cardiomyopathy and NYHA class II or III, there was a statistically significant improvement in ejection fraction (OR 10.15, 95% CI: 1.96 - 52.69, $p = 0.006$). Similarly, the Skudicky et al.[6] (2001) trial also suggests that use of pentoxifylline in the treatment of heart failure may be beneficial, but the effect in this study was not statistically significant (OR 3.42, 95% CI: 0.89 - 13.18, $p = 0.07$). The results of the Sliwa et al.[7] (2002) study point to the significant benefit with the use of pentoxifylline in patients with severe heart failure (i.e. NYHA class IV) due to idiopathic dilated cardiomyopathy (WMD 8.40, 95% CI: 8.32 - 8.48). These findings have been extended to patients with heart failure of varying severity due to ischaemic dilated cardiomyopathy (WMD 8.10, 95% CI: 2.74 - 13.46, $p = 0.003$).[9]

Frequency of hospitalisation

None of the selected trials reported this endpoint.

Mortality

Pentoxifylline was associated with a trend towards reduction in mortality, but this was not statistically significant. In the Skudicky et al.[5] (2000) trial of 49 patients with NYHA II - III heart failure due to idiopathic dilated cardiomyopathy, treatment with pentoxifylline was associated with a potentially large reduction in mortality of 74%, but this was not statistically significant (OR 0.26, 95% CI: 0.05 - 1.45, $p = 0.12$). A similar non-significant trend was found in another group of

39 patients with NYHA class II - III idiopathic dilated cardiomyopathy (OR 0.59, 95% CI: 0.09 - 4.01, $p = 0.6$);[6] 18 patients with NYHA class IV idiopathic dilated cardiomyopathy (OR 0.44, 95% CI: 0.03 - 5.93, $p = 0.5$);[7] and NYHA class I - IV ischaemic dilated cardiomyopathy (OR 0.18, 95% CI: 0.02 - 1.83, $p = 0.15$).[9]

Discussion

We conducted a systematic review of randomised controlled trials in order to determine the effectiveness of pentoxifylline in patients with heart failure. Despite a systematic and thorough search of the available literature, we identified only 4 small randomised controlled trials with a total of 144 patients which tested the effectiveness of pentoxifylline in heart failure.[4-7,9] Our findings suggest that pentoxifylline may be effective in improving the symptoms (measured by NYHA functional class) and cardiac function (measured by LVEF) in people with heart failure due to idiopathic and ischaemic cardiomyopathy. Pentoxifylline also had a promising effect on mortality, but this effect was not statistically significant.

It is important to consider the limitations of the evidence currently available. The existing trials included a small number of patients, suggesting that they may not provide reliable and robust estimates of the effect of pentoxifylline on important outcomes, such as mortality. Although the overall quality of trial design was adequate, randomisation, allocation concealment methods and loss to follow-up were not adequately recorded in all studies. A large multicentre study may be able to overcome the limitations of the present studies, and provide conclusive evidence on the effectiveness of pentoxifylline in reducing the risk of death in people with heart failure.

Implications for practice

On the basis of the currently available evidence, pentoxifylline cannot yet be recommended for routine use in patients with heart failure.

Implications for research

There is a need for a large, multicentre, prospective randomised controlled trial to assess the effectiveness of pentoxifylline in heart failure management. Careful attention ought to be paid to the drug's influence on hard endpoints, such as mortality and frequency of hospitalisation. Such a trial should include patients with heart failure of varying aetiology and severity.

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Can medical scheme reform lead to fairer distribution of limited resources? A funding perspective

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While many South Africans were celebrating 10 years of democracy, frustrated doctors took to the streets to voice their dissatisfaction about the state of health care in our country. Both public and private-sector workers joined the protest against deteriorating working conditions in public facilities, inadequate patient care and various government intervention strategies. Private-sector doctors were motivated in particular by the impending Medicines Control Amendment Act (forcing the special licensing of dispensing doctors) and the proposed Certificate of Need (regulating where doctors may practise in future). Such legislation is perceived as heavy-handed, uninformed and a destructive interference.

Amid such frustration and confrontation, and mindful of arguably inept introduction of some aspects of government policy and legislation, we believe it timely to review some of the positive aspects of recent developments in health care. We refer particularly to changes within the medical scheme environment. Medical scheme legislation has resulted in the unusual, but opportune, situation of private medical schemes and their managed care organisations being governed by principles of social health — a concept, we believe, not widely acknowledged or understood as yet by a majority of stakeholders. Current and proposed legislation has paved the

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way for solidarity and is encouraging improved funding and delivery models of health care, with the ultimate objective of fairer distribution of resources and better access to health care.

Social health insurance (SHI)

South Africa's progressive constitution is highly protective of the individual's socio-economic rights, including the right to have access to 'health service' (Chapter 2, section 27, Constitution of the Republic of South Africa, 1996). There is an obligation on the state's leadership not only to respect and protect the right to health care, but also to implement such a right. Therefore, to facilitate the progressive realisation of quality health care for all, government is committed to a system of SHI.[1] The objectives of such health care funding reform would be to reduce inequities in health care financing by improving cross-subsidisation of the sick and poor by the healthy and wealthy and by increasing revenue through mandatory contributions specifically earmarked for spending on health care services.[2] Funding disparities include the following.

1. Private-sector health care spending is more than 5 times the per capita expenditure of the public sector. Or, presented differently, the private sector spends R35.5 billion to serve only 17% of the population, whereas the other 83% of the population only have R32.2 billion to share.[3]

2. Until recently, there was discrimination within the private sector against the sick and those with lower incomes.

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