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Beta-Blockers and Peripheral Arterial Disease

G. Stark

In patients with large vessel peripheral arterial disease the excess risk of death is due to an increase in deaths from cardiovascular disease, especially coronary heart disease. β-blockers are one of the most powerful drugs in reducing overall cardiovascular mortality. However, β-blockers have been considered to be relatively contraindicated in patients with concomitant intermittent claudication because of the suggested blockade of β_2-receptor mediated skeletal muscle vasodilatation. Pooled estimate of overall treatment effect in meta-analysis did not show any significant effect of β-blockers on pain-free walking distance or maximal walking distance. This finding should be drawn with caution to patients with Raynaud's phenomenon or severe peripheral disease, because in these patients individual responses are less predictable than those from study populations. Nevertheless, β-blockers should be given to patients suffering from peripheral occlusive disease who are at high risk for cardiovascular disease because of its well documented effect on reducing overall cardiovascular mortality. *J Clin Basic Cardiol 2001; 4: 15–16.*

Key words: beta-blocker, peripheral arterial disease, Raynaud's phenomenon, pain-free walking distance

In patients with large vessel peripheral arterial disease the excess risk of death is due almost entirely to an increase in death from cardiovascular disease, especially coronary heart disease. The distribution of risk factors among subjects with and without cardiovascular disease overlap considerably and the presence of large-vessel peripheral arterial disease may reflect a particular susceptibility to the development of atherosclerosis. Risk factors such as cigarette smoking, impaired glucose tolerance and hypertension are particularly associated with an increased risk of developing intermittent claudication [1–3].

Recommendations for Beta-Blocker Treatment in Patients with Intermittent Claudication

Hypertension, particularly elevated systolic blood pressure, has been reported to increase the risk of intermittent claudication in men and women by 2.4- to 3.9-fold [3]. Persons over 60 years of age have the highest prevalence of peripheral vascular disease which is closely associated with coronary artery disease and hypertension. Of all the available pharmacologic agents to treat coronary artery disease and hypertension, β-blockers have been considered to be relatively contraindicated in patients with concomitant intermittent claudication. The fact that β-blockers diminish cardiac output and the suggested blockade of β_2-receptor mediated skeletal muscle vasodilatation have been some of the few hypothetical mechanisms used to support the claimed adverse effects and cautious recommendations [4–6].

The background for these recommendations are uncontrolled observations of intermittent claudication and vasospastic phenomena associated with the use of β-blockers [7–9]. Data from controlled clinical trials generally show no important clinical deleterious effects of β-blockers on intermittent claudication or pain-free walking distance [10–12]. The published evidence is mixed in terms of design, execution and the choice and outcome of clinical end-points. Consequently, uncertainty regarding β-blocker therapy in subjects with intermittent claudication still remains.

Results of Meta-Analyses of Controlled Trials

The best way out of this dilemma is shown by results of meta-analyses of randomised controlled trials dealing with beta-blocker therapy in subjects with peripheral arterial disease. In the paper of Kenneth et al. [13] they analysed all randomised controlled trials comparing β-blockers with placebo or a non-placebo control performed between 1966 and 1990. Only four reports in this meta-analysis included seven controlled β-blocker studies that provided data for an analysis of pain-free walking distance [11, 14–16]. In two studies where patients received metoprolol the walking distance slightly increased in comparison to placebo [15, 16]. For pindolol and labetalol, but not for atenolol, a statistically significant reduction in pain free-walking distance was reported [11]. A pooled estimate of overall treatment effect in this meta-analysis did not show any significant effect of β-blockers on pain-free walking distance or maximal walking distance. For pain-free walking distance, the results indicate that the walking capacity of the average patient receiving a β-blocker was approximately 0.25 SD less than that of the average control subject. Despite the lack of statistical significance, however, it should be acknowledged that the average subject receiving a β-blocker did show an overall slight negative change in pain free walking capacity.

Nevertheless, the major findings indicate that beta-blockers do not adversely affect walking capacity or lead to worsening of intermittent claudication. Despite the variations in treatment duration, choice of clinical end-points and type of beta-blockers, nearly all investigators concluded that β-blockers, compared with placebo, had no clinically important or statistically significant adverse impact on walking capacity or symptoms of intermittent claudication. These results are in contrast to uncontrolled reports that have led to cautious recommendations and the clinical impression that β-blockers may precipitate intermittent claudication in patients with peripheral vascular disease [17].

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Conclusions

The missing effects of β-blockers on walking capacity were consistent in multiple studies conducted over more than 25 years in different settings and, therefore, strengthen the conclusion that β-blockers may not worsen intermittent claudication. However, these conclusions should be applied with caution to patients with Raynaud's phenomenon or severe peripheral disease, because in these patients individual responses are less predictable than those from study populations.

As mentioned at the beginning, in patients with large vessel peripheral arterial disease the excess risk of death is due to an increase in deaths from cardiovascular disease, especially coronary heart disease. β-blockers are one of the most powerful drugs in reducing overall cardiovascular mortality. Because of this fact, medical practitioners should be encouraged to give β-blockers also to patients suffering from peripheral occlusive disease who are at high risk for cardiovascular disease.

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