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Research report

Beta blocker therapy is associated with reduced depressive symptoms 12 months post percutaneous coronary intervention

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ABSTRACT

Background: Beta blocker therapy may induce depressive symptoms, although current evidence is conflicting. We examined the association between beta blocker therapy and depressive symptoms in percutaneous coronary intervention (PCI) patients and the extent to which there is a dose–response relationship between beta blocker dose and depressive symptoms.

Methods: Patients treated with PCI (N = 685) completed the depression scale of the Hospital Anxiety and Depression Scale 1 and 12 months post PCI. Information about type and dose of beta blocker use was extracted from medical records.

Results: Of all patients, 68% (466/685) were on beta blocker therapy at baseline. In adjusted analysis, beta blocker use at 1 month post PCI (OR: 0.82; 95% CI: 0.53–1.26) was not significantly associated with depressive symptoms. At 12 months post PCI, there was a significant relationship between beta blocker use and depressive symptoms (OR: 0.51; 95% CI: 0.31–0.84), with beta blocker therapy associated with a 49% risk reduction in depressive symptoms. There was a dose–response relationship between beta blocker dose and depressive symptoms 12 months post PCI, with the risk reduction in depressive symptoms in relation to a low dose being 36% (OR: 0.64; 95% CI: 0.37–1.10) and 58% (OR: 0.42; 95% CI: 0.24–0.76) in relation to a high dose.

Conclusions: Patients treated with beta blocker therapy were less likely to experience depressive symptoms 12 months post PCI, with there being a dose–response relationship with a higher dose providing a more pronounced protective effect.

1. Introduction

Beta blocker therapy has clear survival benefits in patients with chronic heart failure (Javed and Deedwania, 2009), in patients following a myocardial infarction (MI), and in patients with hypertropic obstructive cardiomyopathy (Bangalore et al., 2007). Beta blockers are also used in the treatment of supraventricular arrhythmias, to control ventricular arrhythmias related to sympathetic activation, and to prevent postoperative cardiac complications during noncardiac surgery (Bangalore et al., 2007). Beta blockers are prescribed not only for cardiovascular disease but also for migraine prophylaxis, various anxiety disorders, tremor, and aggressive disorders secondary to organic brain illnesses (Elliott, 1977; Jankovic and Fahn, 1980).

There has been a long-standing concern, however, that beta blocker use might be associated with neuropsychological side effects, such as depression. In 1967 Waal already reported a 50% incidence of depression in patients prescribed more than 120 mg/day of propranolol for hypertension, although this

Abbreviations: AP, angina pectoris;CAD, coronary artery disease;CNS, central nervous system;HADS, Hospital Anxiety and Depression Scale;MI, myocardial infarction;OR, odds ratio;PCI, percutaneous coronary intervention

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finding was largely based on anecdotal evidence (Waal, 1967). Experts have suggested that the inhibitory actions of beta blockers on the beta receptors and serotonin receptors in the central nervous system may be involved in the pathophysiology of depressive disorders (1977). However, subsequent publications have reported conflicting results (Avorn et al., 1986; Bright and Everitt, 1992; Ko et al., 2002; Krantz et al., 1982; Patten and Love, 1993; Schleifer et al., 1991; Thiessen et al., 1990). These conflicting results may in part be attributed to differences in study design and case definition, and in part to confounding disease states (Ried et al., 1998). A more recent and well conducted study that used a prospective design showed no relationship between beta blocker use and depression — neither depressive symptoms nor depressive disorder (van Melle et al., 2006). A review by Verbeek et al. did not ruled out that specific types of beta blockers might have a depressogenic effect but this weak evidence should not be decisive to prescribe beta blockers to patients (Verbeek et al., 2011).

Given that depression is associated with a 2-fold risk of mortality in patients with coronary artery disease (CAD) (Nicholson et al., 2006), and even minimal symptoms of depression have been shown to predict short-term prognosis in patients treated with percutaneous coronary intervention (PCI) with drug eluting stenting (Pedersen et al., 2009), it is important to know whether beta blocker therapy is linked to depression.

We examined the association between beta blocker therapy and depressive symptoms in patients treated with PCI and the extent to which there is a dose–response relationship between beta blocker dose and depressive symptoms.

2. Methods

2.1. Patient population and design

The study population (N = 685) consisted of two cohorts, all were treated with the Taxus stent. Patients were enrolled in the study if they were at least 18 years of age, had stable or unstable angina or provokable ischemia, and were undergoing PCI for a single, previously untreated lesion in a native coronary artery (Stone et al., 2004). The exclusion criteria were PCI for a lesion involving a previously implanted stent or patients receiving only BMS in the DES era (Stone et al., 2004). Depressive symptoms were assessed within 1 month post PCI (referred to as baseline in the remainder of the article) and 12 months post PCI in both cohorts.

The first consecutive cohort (cohort I) was comprised of 406 patients treated with PCI between July 1, 2003 and July 1, 2004. These patients completed the Hospital Anxiety and Depression Scale (HADS) at baseline and 12 months post PCI. Only patients who completed the HADS at baseline as well as 12 months post PCI were included in this study. Differences on baseline characteristics between responders and excluded/non-responders were found on age and diabetes. Excluded and non-responders were more likely to be older (mean age = 64 ± 10 vs. 62 ± 11) but less likely to have diabetes (15% versus 19%). No other systematic differences were found on baseline characteristics, including cardiac medication.

The second consecutive cohort (cohort II) included 279 patients treated with PCI between January 2006 and August 2006, who completed the HADS at baseline and 12 months post PCI. Only patients who completed the HADS at baseline as well as 12 months post PCI were included in this study. Differences on baseline characteristics between responders and excluded/non-responders were found on age and prior PCI. Excluded and non-responders were more likely to be younger (mean age = 61 ± 11 vs. 63 ± 11) but less likely to have undergone a prior PCI (23% versus 28%). No other systematic differences were found on baseline characteristics, including cardiac medication.

Differences between Cohorts I and II were the following. Patients enrolled in cohort I were more likely to have hypercholesterolemia, a prior MI, a PCI indication for stable AP, and they were more likely on a beta blocker, calcium antagonist, ACE inhibitor and diuretics. Furthermore, there were fewer smokers in Cohort I.

2.2. Demographic and clinical variables

Information on demographic and clinical variables was obtained from the patients' medical records or from purpose-designed questions in the questionnaire. Demographic variables included age and gender. Clinical variables included cardiac history (i.e., previous MI, PCI or coronary artery bypass graft surgery (CABG)), indication for PCI (MI, stable or unstable angina), stent type (sirolimus eluting stent or paclitaxel-eluting stent) smoking status, hypertension, hypercholesterolemia, diabetes, familiar cardiac history and multivessel disease. Cardiac medication included aspirin, beta blockers, calcium antagonists, nitrates, ACE inhibitors, and statins. Information on all the clinical variables was collected during and immediately after the procedure.

Given the objective of the study, we collected detailed information on both the type of beta blocker used and the dose. Types of beta blockers prescribed included bisoprolol, metoprolol, atenolol, carvedilol, nebivolol, propranolol, labetolol, pindolol, sotalol, and celiprolol. Dose of beta blocker therapy was divided into low versus high, with a low dose defined as patients using less than 25% of the maximum recommended therapeutic dose, whereas a high dose was defined as exceeding or equal to 25% of the maximum recommended therapeutic dose (van Gestel et al., 2008). For bisoprolol, a maximum recommended therapeutic dose of 20 mg was used, for metoprolol 400 mg, for atenolol 100 mg, for carvedilol 50 mg, for nebivolol 10 mg, for propranolol 320 mg, for labetolol 800 mg, for pindolol 30 mg, for sotalol 320 mg, and for celiprolol 400 mg.

2.3. Depressive symptoms

Depressive symptoms were assessed with the 7-item depression subscale of the Hospital Anxiety and Depression Scale (HADS) (Bjelland et al., 2002). All items are answered on a four-point Likert scale from 0 to 3 with a score range of 0–21, with a higher score indicating more depressive symptomatology. Depressive symptoms were dichotomized using the standardized cut-off ≥ 8. The HADS is a valid and internally consistent measure, as indicated by Cronbach's $\alpha = 0.68$–0.93 for anxiety and Cronbach's $\alpha = 0.67$–0.90 for depressive symptoms (Bjelland et al., 2002). An advantage of using HADS in cardiac patients is that the scale contains no somatic items, decreasing the likelihood that scores are confounded by disease severity (Herrmann-Lingen et al., 2001).