SCIENTIFIC LETTER

Metoprolol prophylaxis against postoperative atrial fibrillation increases length of hospital stay in patients not on pre-operative β blockers: the β blocker length of stay (BLOS) trial

E Crystal, K E Thorpe, S J Connolly, A Lamy, I Cybulsky, S Carroll, R Roberts, M Gent

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Postoperative atrial fibrillation (AF) is a common complication of heart surgery, affecting 20–40% of patients. In recent guidelines of the American Heart Association and the European Society of Cardiology, β blocker (BB) treatment has been recommended as a first line choice for the prevention of postoperative AF.[1] Although the efficacy of re-administration of BB to post-cardiac surgery patients has been evaluated, the effectiveness of prophylactic BB in patients without prior BB treatment has not been adequately studied.

In order to evaluate whether preoperative BB use affects the outcome of prophylactic BB treatment after heart surgery, an analysis was performed using the data of the largest double blind, placebo controlled, randomised trial of prophylactic BB treatment (metoprolol) for reduction in hospital length of stay following heart surgery, known as the β blocker length of stay (BLOS) study.[2]

In the BLOS study 1000 patients undergoing elective open heart surgery were randomised equally to metoprolol (100–150 mg/day) or double blind placebo, started within 12 hours of arrival in the intensive care unit (ICU) after surgery. The patients were followed for postoperative AF, length of hospital stay, and cost of in-hospital care. A third party payer prospective (Ministry of Health of Canada) was chosen for the cost analysis; costs are quoted in Canadian dollars.

The central question this study addresses is: ''Does the therapeutic effect of prophylactic metoprolol use differ according to preoperative BB usage?'' Multiple linear regression was used for quantitative outcomes such as length of stay, and multiple logistic regression was used for discrete outcomes such as AF. Tests of interaction were done to assess whether the effect of treatment differed significantly between two different groups of patients. Fisher's exact test and Student's *t* test (both two sided) were used to compare baseline characteristics between the two preoperative BB usage groups.

RESULTS

Of 1000 patients enrolled in the BLOS study, 806 patients (81%) received a BB preoperatively and 194 (19%) did not (BB and no BB groups, respectively). The groups were similar in age, sex, and history of AF (table 1). More patients in the BB group had received diltiazem before surgery (34.5% *v* 16.3%, $p < 0.001$) and more patients in the BB group underwent coronary artery bypass grafting (CABG), compared to the no BB group (who were more likely to have other valve or combined surgery) (92.1% *v* 55.7%, $p < 0.001$). The haemodynamic response to prophylactic metoprolol was different in the two groups (table 1). The no BB patients showed a significantly greater decrease in cardiac index and a greater negative chronotropic effect with metoprolol.

In the whole study population, prophylactic metoprolol reduced the percentage of patients in whom AF occurred from 39% to 31% (relative risk reduction of 20%, $p < 0.01$). In the BB group, metoprolol decreased the occurrence of postoperative AF from 40.1% to 29.6%; however, in the no BB group, the risk of AF increased from 35% to 38.5% ($p = 0.065$, after adjustment for age and type of surgery, $p = 0.3$).

Abbreviations: AF, atrial fibrillation; BB, β blocker; BLOS, β blocker length of stay; CABG, coronary artery bypass grafting; ICU, intensive care unit

Table 1 Physiologic response to study drug administration

		Study drug			
	Pre-operative BB	Metoprolol	Placebo	Difference between placebo and metoprolol	*p Value
Change between baseline and 8 hours in ICU					
Heart rate	Yes	−2.39 (9.80)	−0.41 (9.05)	1.98 (9.44)	0.0022
	No	−5.74 (11.42)	1.03 (9.87)	6.77 (10.61)	
Cardiac index	Yes	−0.13 (0.67)	−0.082 (0.64)	0.051 (0.66)	0.0018
	No	−0.34 (0.80)	−0.016 (0.72)	0.32 (0.76)	
PAWP	Yes	0.51 (3.32)	−0.45 (3.23)	−0.96 (3.28)	0.17
	No	0.61 (3.68)	0.41 (3.15)	−0.19 (3.41)	
Change between baseline and day 4					
Heart rate	Yes	−4.27 (16.43)	4.98 (17.20)	9.25 (16.82)	0.50
	No	−5.93 (16.45)	1.11 (14.47)	7.04 (15.46)	

Figures are presented as mean and standard deviation of mean.
*Unadjusted p values of interaction (p value tests for an interaction between pre-operative BB use and study drug).
BB, β blocker; ICU, intensive care unit; PAWP, pulmonary artery wedge pressure.

Table 2 Occurrence of postoperative AF, length of stay in ICU, and total length of stay in hospital

	Pre-operative BB	Study drug: Metoprolol	Study drug: Placebo	Odds ratio	Difference between placebo and metoprolol	p Value*
Dichotomous outcomes						
AF	Yes	29.6%	40.1%	0.63		0.065
	No	38.5%	35.0%	1.16		
Complications†	Yes	8.8%	7.8%	1.14		0.99
	No	12.1%	10.7%	1.15		
Continuous outcomes						
ICU stay (hours)	Yes	36.1 (30.8)	34.9 (25.8)		−1.2 (28.5)	0.03‡
	No	53.0 (107.8)	31.7 (18.1)		−21.3 (75)	
Hospital stay (hours)	Yes	149.2 (57.2)	152.4 (61.7)		3.3 (59.4)	0.002‡
	No	183.4 (171.2)	148.0 (59.2)		−35.4 (124.9)	
Hospital cost (C$)	Yes	4755 (2040)	4729 (1730)			
	No	5374 (2839)	4521 (1508)			

BB, β blocker; ICU, intensive care unit
*Unadjusted p values of interaction (p value tests for an interaction between pre-operative BB use and study drug).
†Complications were: ventricular tachyarrhythmia, stroke, myocardial infarction, embolism, infection, need for a permanent pacemaker, ventilation for >3 days or reintubation.
‡p value calculated after taking logarithm base 10.

Overall, metoprolol did not significantly affect either the length of stay in the ICU or length of stay in hospital. However, the effect of prophylactic metoprolol on length of stay differed significantly between patients in the BB and the no BB groups (table 2). For patients in the BB group, length of stay in the ICU and total length of stay were essentially unaffected by metoprolol. For patients in the no BB group, prophylactic metoprolol increased mean (SD) length of stay in the ICU from 31.7 (18.1) to 53.0 (107.8) hours ($p = 0.03$). There was an increase for total length of stay from 148.0 (59.0) to 183.4 (171.2) hours ($p = 0.002$). These differences in metoprolol effect between groups remained significant after adjustment for differences in baseline characteristics. The significant interaction between prophylactic metoprolol and preoperative use of BB suggests that prophylactic metoprolol affects these patient populations differently.

The rate of complications was low and not different between study groups (table 2). The hospital costs were not affected by prophylactic metoprolol in the BB group (mean (SD) C$4755 (2040) *v* C$4729 (1730)), but were significantly increased by prophylactic metoprolol in patients of the no BB group (C$5374 (2839) *v* C$4521 (1508), $p = 0.009$).

DISCUSSION

Patients not previously on BB received no benefit from prophylactic metoprolol and appear to have had worse outcomes in terms of haemodynamics, length of stay in hospital, and costs.

This observation is biologically plausible as BB withdrawal is known to create a hyperadrenergic state. If preoperative BB use is important for the benefits of prophylactic BB treatment to occur, then in patients without BB withdrawal (without history of preoperative BB treatment), the potential to achieve a benefit is lessened. However, the potential for BB related side effects remains.

Essentially, patients having CABG in our study were more likely to have received a BB preoperatively than those having valve surgery. It is unlikely that the different ratio of valve to CABG surgery between groups explains the observation of this paper. It is possible that unrecognised contraindications for BB were missed at the time of enrolment into the study, but this is unlikely given the same proportions of patients ventilated for more than three days, reintubated, or requiring a permanent pacemaker.

This study indicates that only patients with a history of BB use before the operation appear to benefit from such prophylaxis. Patients not on BB preoperatively might be considered for prophylaxis by alternative drugs or for no prophylaxis. These findings are not conclusive but are hypothesis generating and should be tested in further prospective trials.

Authors' affiliations

E Crystal, Division of Cardiology, Sunnybrook and Womens' College Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada
K E Thorpe, R Roberts, M Gent, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada
S J Connolly, S Carroll, Department of Medicine, McMaster University
A Lamy, I Cybulsky, Department of Surgery, McMaster University

Correspondence to: Dr Eugene Crystal, 2075 Bayview Avenue, Room D377, Division of Cardiology, Sunnybrook and Womens' College Health Science Centre, Toronto, Ontario, Canada; eugene.crystal@sw.on.ca

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