MULTICENTERED TRIAL OF TEZOSENTAN IN CARDIAC SURGERY

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Cardiopulmonary bypass (CPB)-induced elevations in circulating endothelin levels are associated with post-operative pulmonary hypertension (PH), right ventricular failure and increased patient mortality following cardiac surgery. These effects may acutely worsen pre-existing PH in patients undergoing cardiac surgery. Endothelin receptor antagonists, such as tezosentan, may mitigate CPB-induced PH, reducing the incidence of right ventricular failure and associated mortality.

The protocol was reviewed and approved by the Research and Ethic Committees of each institution. Written informed consent was obtained from all patients. In this multicenter, double-blind, randomized, placebo-controlled trial, eligible patients aged ≥18 years with significant documented PH scheduled to undergo cardiac surgery were randomized (1:1) to receive i.v. tezosentan (5 mg/h) during surgery and afterwards for up to 24 hours (1 mg/h), or matched placebo infusion. The primary efficacy endpoint was the proportion of patients with clinically relevant right ventricular failure during weaning from CPB, which was assessed 30 min after the end of CPB. Safety was assessed by means of treatment-emergent adverse events, serious adverse events and deaths.

Two hundred and seventy-four patients received tezosentan (n = 133) or placebo (n = 141). There was no difference between the two groups with respect to the primary endpoint; 14 patients in the tezosentan group (10.5%) and 16 patients in the placebo group (11.3%) had clinically-relevant right ventricular failure (treatment effect: 0.07 [95% CI -0.83, 0.53; p = 0.8491]). Similarly, there was no difference between the percentage of patients who had a major clinical event, in the time to weaning from CPB or time from end of CPB to final discharge from intensive care. The incidence of treatment-emergent adverse events and serious adverse events was also comparable between the two groups and rarely led to discontinuation. None of the three deaths (tezosentan, n = 1; placebo, n = 2) that occurred within 24 h of weaning from CPB was considered related to study medication.

A reduction in clinically-relevant right ventricular failure with tezosentan was not observed in this study. Safety findings were consistent with those reported previously with tezosentan in patients with acute heart failure and there was no indication of adverse outcomes with tezosentan.

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