Effects of prophylactic indomethacin treatment on postoperative pericardial effusion after aortic surgery

Mustafa Bahadir Inan, MD, Levent Yazıcıoglu, MD, Sadik Eryılmaz, MD, Mustafa Sırlak, MD, Demir Cetıntas, MD, Bulent Kaya, MD, and Umit Ozyurda, MD

Objective: This prospective, randomized study assessed the prophylactic effects of indomethacin treatment on pericardial effusion after aortic surgery.

Methods: Eighty-five patients were found eligible to participate in this double-blind study. Patients were assigned to a control group receiving oral placebo or to an indomethacin group receiving 25 mg oral indomethacin 3 times daily for 7 days preoperatively. After aortic surgery, patients were followed up clinically and evaluated for pericardial effusion with transthoracic echocardiography on the first and seventh postoperative days during hospitalization and at the second and sixth weeks after discharge.

Results: The demographic and the operative data were similar between groups. The surgical interventions included Bentall procedure in 63 patients, valve-sparing procedures in 7 patients, and supracoronary ascending aorta replacement in 15 patients. Hemiarch replacement was performed in 16 patients. No patient in either group had pericardial effusion after the first postoperative day. At the end of the first week, however, 2 patients had pericardial effusion, at the end of the second week after discharge, 3 patients had pericardial effusion, and at the end of the sixth week after discharge, 4 patients had PEs. One of the patients who had PE at the end of the sixth week received indomethacin; the others were all in the control group, a significant difference ($P = .019$). Five patients underwent transthoracic echocardiographically guided pericardiocentesis; 4 underwent surgical pericardiocentesis.

Conclusions: Indomethacin may have beneficial effects on the outcomes and incidence of postoperative pericardial effusion after aortic surgery. (J Thorac Cardiovasc Surg 2011;141:578-82)

Pericardial effusion (PE) is not uncommon after cardiac surgery. Depending on the methodology used for its detection, PE has been reported in 1% to 6% of patients.[1,2] Although it is generally reversible and not life threatening, it may evolve toward cardiac tamponade, a potentially lethal complication.[3]

Surgery involving the ascending aorta may result in higher incidence of PE and cardiac tamponade relative to other cardiac surgical procedures (up to 31.6% and 15.7%, respectively). Prolonged cardiopulmonary bypass (CPB) and extensive dissection of the heart and the aorta are the main causes of increased incidence in aortic surgery.[2,4]

PEs after aortic surgery are often loculated, forming along the posterior left ventricular wall.[5,6] They are often small in amount and benign, but they may be circumferential and quite large (which may impede cardiac filling, reduce cardiac output, and lead to tamponade) or regional and located in a strategic area incriminated in the development of arrhythmias.[7,8]

The best management of the large PE is controversial. Some authors advise routine pericardial drainage by pericardiocentesis or surgical pericardiotomy irrespective of the presence of tamponade, claiming diagnostic and therapeutic benefits.[9,10] Although these procedures are generally well tolerated, they are not innocuous, and some fatalities have been reported. In addition, it is sometimes impossible to drain the effusion completely because of a loculated pattern.[10]

As well as surgical treatment, a variety of pharmacologic agents have been used to treat PE and pericarditis, including nonsteroidal anti-inflammatory drugs and steroids.[11-14] Because of the multifactorial etiology of postoperative effusion and the well-known inflammatory response to CPB, indomethacin, with its ability to inhibit inflammatory mediators, could have a beneficial effect in decreasing PE after cardiac surgery. Reports have described the effects of indomethacin in acute or uremic pericarditis[12-15] and in cardiac tamponade.[16] In these studies, the indomethacin dosage was kept between 75 and 150 mg daily. On the basis of this hypothesis, this prospective, randomized study was planned to assess the effects of prophylactic indomethacin treatment on postoperative PE after aortic surgery.

MATERIALS AND METHODS

From February 2005 to May 2009, a total of 87 patients were screened and randomly allocated for participation in this study. Inclusion criteria consisted of informed consent, first-time repair of the ascending aorta with or

From the Department of Cardiovascular Surgery, Ankara University School of Medicine, Ankara, Turkey.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Sept 7, 2009; revisions received Feb 20, 2010; accepted for publication March 14, 2010; available ahead of print April 23, 2010.

Address for reprints: Mustafa Bahadir Inan, MD, Ankara University Medical School, Department of Cardiovascular Surgery, Cardiac Center Cebeci, Ankara, Turkey (E-mail: mbahadirinan@gmail.com).

0022-5223/$36.00

doi:10.1016/j.jtcvs.2010.03.021

Abbreviations and Acronyms
CPB = cardiopulmonary bypass
INR = international normalized ratio
PE = pericardial effusion
TTE = transthoracic echocardiography

without aortic valve replacement, and diagnosis of type A dissection or ascending aortic aneurysms. Exclusion criteria included preoperative effusion, previous gastrointestinal bleeding, cardiac failure, kidney failure, infections, hematologic disorders, receipt of anti-inflammatory drugs before hospitalization, indomethacin allergy, requirement for additional procedures such as coronary artery bypass grafting, valvular operations involving the mitral or tricuspid valve or left ventricular aneurysmectomy, urgent operations, emergency operations on patients who had received indomethacin for less than 7 days, refusal to participate in the study, participation in another investigational protocol, intraoperative or early in-hospital death, and prolonged postoperative ventilation.

Written, informed consent was obtained from each patient before starting the study, and the protocol was approved by the local ethics committee. The study was a double-blind protocol in which the surgical staff, principal investigators, and patients were blinded to the assigned therapy. Clinical data were collected and recorded in the database by independent, blinded investigators.

Patients were randomly assigned in a double-blind fashion either to a control group receiving oral placebo or to an indomethacin group receiving 25 mg oral indomethacin 3 times daily for 7 days before the operation. Daily administration of 75 mg indomethacin is an average dose used in previous studies and was the dose most used in the treatment of pericarditis[12-15] and cardiac tamponade.16 The same medication was continued for 6 weeks after the operation.

Standardized anesthesia and surgical protocols were applied, and all the operations were performed with CPB. Additionally, in some cases total circulatory arrest was established. After the main aortic surgical procedure, a 36F conventional drain was placed retrosternally in the anterior mediastinum overlying the heart and a 16F thin, closed-suction drain system was placed toward the posterior pericardial cavity.

All the patients received heparin to have achieved an activated clothing time of about 200 seconds in the first 24 hours and were switched to low–molecular weight heparin for approximately 3 days. Patients who underwent aortic valve replacement also received warfarin, and the international normalized ratio (INR) was kept between 2 and 2.5.

The larger mediastinal drains were removed on the first postoperative day. The thinner drains were kept until the daily drainage was less than 50 mL in 24 hours.

Patients were kept in the intensive care unit and moved to the ward if the follow-up was uneventful. Transthoracic echocardiography (TTE) was performed on the 1st and 7th postoperative days, and patients were evaluated for PE. PE was classified as anterior, posterior, or circumferential, and PEs larger than 10 mm were considered as significant. PE diagnosed in the first postoperative week was defined as early, with any developing after the first week defined as late.[2] In addition to TTE, routine radiographs and blood tests, including determination of INR, were carried out. Patients were discharged at the end of an uneventful ward follow-up.

Patients were called at the end of the second and sixth weeks, and telecardiography, blood counts, C-reactive protein, and INR were studied. Additional TTE was performed at these times.

Statistical Analysis

Categoric variables are described as percentages and frequencies. Groups were compared with Pearson χ^2 and Fisher's Exact tests. Comparisons between groups were done with the Mann–Whitney U test.

RESULTS

Of the 87 patients found eligible to participate in the study, 2 were excluded because of surgical mortality and prolonged ventilation, leaving 85 patients (47 male and 38 female) for analysis. The mean ages of the patients were 50.3 ± 8.3 years (35–77 years) in the indomethacin group and 47.8 ± 9.9 years (29–72 years) in the control group. Patient characteristics are reported in Table 1.

The spectrum of surgical interventions included Bentall procedure (aortic root replacement with an aortic valve replacement with a composite valve–graft conduit) in 63 cases, valve-sparing procedures (aortic valve repair and ascending aorta replacement with a tubular Dacron polyester fabric graft) in 7 cases, and isolated supracoronary ascending aorta replacement with a tubular Dacron polyester fabric graft in 15 cases. Sixteen of all patients also underwent hemiarch replacement. There were no significant differences between the groups with regard to types of surgical procedures (Table 2).

All the operations were performed with CPB, and 24 patients (10 in the indomethacin group and 14 in the control group) were operated on with deep hypothermic cardiac arrest. The crossclamp, CPB, and hypothermic arrest durations were similar between groups. The operative data are summarized in Table 2.

Two patients in the indomethacin group and 3 in the control group underwent reexploration for bleeding. Amount of postoperative bleeding and amounts of blood and blood products used are listed in Table 2.

Durations of thinner drains were 49.1 ± 5.3 hours in the indomethacin group and 51.3 ± 7.4 hours in the control group. This difference was insignificant (Table 2). The mean INR results, which were similar, are given in Table 2.

No patients in either group had PE after the first postoperative day. Two patients in the control group, however, had significant early PE at the end of the first week. Both these patients underwent TTE-guided pericardiocentesis. At the end of the second week after discharge, 3 patients, all in the control group, had significant PE. Two patients underwent surgical pericardiocentesis; the other patient underwent TTE-guided pericardiocentesis. At the end of the sixth week, late PE was present in 1 patient in the indomethacin group and 3 patients in the control group. Two underwent surgical pericardiocentesis through a subxiphoid approach, and the remaining 2 were treated with TTE-guided pericardiocentesis. During hospitalization and follow-up 8 patients in the control group and only 1 patient in the indomethacin group had significant PE, a significant difference ($P = .019$). Five of these 9 patients had posterior PE, 2 had circumferential PE, and the remaining 2 had anterior PE (Table 2).