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Role of methylprednisolone in the prevention of postpericardiotomy syndrome after cardiac surgery

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Abstract. – OBJECTIVE: Postpericardiotomy syndrome (PPS) occurs in 10-40% of patients after cardiac operations. Pericardial effusions and tamponade occurring > 7 days after surgery are usually related to PPS and remain an important cause of cardiac surgery-related morbidity and mortality; therefore, preventing PPS is important. Colchicine affords safe and efficacious protection against PPS and related complications. However, the roles of corticosteroids and nonsteroidal anti-inflammatory drugs in PPS prevention remains unclear. This study aimed to determine whether the intraoperative use of single-dose methylprednisolone can effectively prevent PPS.

PATIENTS AND METHODS: This retrospective study included 100 patients undergoing elective coronary artery bypass grafting (CABG) who received a single intraoperative dose of 1 mg/kg methylprednisolone. A further 100 patients undergoing CABG, who were not given methylprednisolone, comprised the control group. The presence and severity of pericardial effusion was determined by echocardiography, with chest X-ray used to assess pleural effusion.

RESULTS: PPS occurrence and pericardial effusion occurrence were significantly lower in patients who received methylprednisolone (p = 0.02 and p = 0.007 respectively). Although the differences were not statistically significant, pericardial and pleural effusions were more severe in the control group than in the methylprednisolone group. Logistic regression analysis demonstrated that methylprednisolone administration was independently associated with prevention of PPS (OR 0.8, 95% CI 0.25-0.91, p < 0.026).

CONCLUSIONS: Intraoperative, single-dose methylprednisolone may confer protection against PPS in patients undergoing CABG.

Key Words:
Coronary artery bypass, Methylprednisolone, Postpericardiotomy syndrome.

Introduction

Pericardial effusion represents a common postoperative complication of, and an important cause of morbidity after cardiac surgery. The pericardial effusion occurrence following cardiac surgery is reportedly between 50-85%[1,2].

In the first week after surgery, pericardial effusions can result from surgical bleeding and perioperative trauma. Pericardial effusions occurring > 7 days after surgery are usually related to postpericardiotomy syndrome (PPS)[3]. PPS occurs in 10-40% of patients after cardiac operations[3,4]. Typically, tamponade develops 1-2 weeks postoperatively (late pericardial tamponade), usually following discharge from hospital[3,4]. The reported prevalence of late pericardial tamponade after cardiac surgery varies among studies (0.8-8.5%) and may be life-threatening[5,6]. Therefore, PPS prevention can reduce pericardial effusion-related postoperative morbidity and mortality.

The inflammatory response that appears during coronary artery bypass grafting (CABG) is related to general surgical trauma. The release of immune mediators is further enhanced by cardiopulmonary bypass (CPB) surgery. The systemic inflammatory response is an important cause of organ dysfunction and can affect patient outcomes. PPS is an autoimmune disorder triggered by cardiac antigen exposure[7-13]. Therefore, reducing the systemic in-

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flammatory response should also reduce the morbidity associated with cardiac surgery and CPB, including PPS occurrence.

Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine and corticosteroids are widely used to manage postoperative pericardial effusions and PPS. To date, few studies have examined the efficacies of pharmacological approaches for the prevention of PPS following cardiac surgery[3,14-16]. Colchicine confers safe and efficacious protection against PPS and related complications[17-20]. Corticosteroids are commonly used in the treatment of autoimmune diseases, and to reduce the inflammatory response associated with CPB and cardiac surgery; the resultant clinical benefits include improvements in postoperative hemodynamics[21], pulmonary function[21], myocardial function and protection[21,22], and reduced length of stay in intensive care units. However, the role of corticosteroids in PPS prevention remains unclear.

This study aimed to determine whether intraoperative use of single-dose methylprednisolone can effectively prevent PPS.

Patients and Methods

Patients

The study was approved by our local Ethics Committee and complies with the requirements of the Declaration of Helsinki. We retrospectively reviewed the medical records of patients who underwent elective, first-time CABG with CPB between January 2012 and June 2014. A total of 100 patients who received a single intraoperative dose of 1 mg/kg methylprednisolone were included, with a further 100 patients undergoing CABG, who were not given methylprednisolone, comprising the control group.

The following exclusion criteria were applied: (1) gastroduodenal ulcer; (2) gastrointestinal hemorrhage; (3) renal failure; (4) hepatic failure; (5) hematological disorders; (6) rheumatic heart disease; (7) emergency procedures; (8) poor ventricular function; (9) redo-CABG; (10) off-pump CABG; (11) surgery within the first week post-infarction; (12) preoperative myocardial infarction; (13) no postoperative echocardiography data available; (14) postoperative effusion in the first week post-surgery; (15) treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) during the postoperative period; and (16) contraindications to corticosteroids.

The primary endpoint was the occurrence of PPS and cardiac tamponade. PPS was diagnosed when patients met at least two of the following five criteria: unexplained postoperative fever persisting for > 1 week postoperatively, pleuritic chest pain, a pericardial or pleural friction rub, a new pleural effusion, or a new pericardial effusion after surgery[3].

Data Collection

Demographic, clinical, and laboratory data were collected from patients' medical records. All chest X-rays and echocardiograms were reassessed, and temperatures were noted.

Transthoracic echocardiography and chest X-ray were performed before discharge and on postoperative day 15 ± 1, in all patients, as a part of our standard postoperative management protocol. Pericardial effusion was sought by echocardiography. In our hospital, pericardial effusion is evaluated in all available echo windows and measured during the diastolic cardiac phase. Effusion size was graded as follows: mild (echo-free space in diastole < 10 mm); moderate (10-20 mm); and large (> 20 mm). Cardiac tamponade was defined as a hemodynamically significant cardiac compression caused by pericardial fluid. Late pericardial tamponade was defined as a pericardial effusion occurring > 7 days postoperatively. The existence and severity of pleural effusion was determined by chest X-ray. Pleural effusion size was graded as follows: below the level of the diaphragm; < 25% of the thorax; and > 25% of the thorax.

To mitigate the inflammatory response to CPB and cardiac surgery, and to reduce morbidity related to the inflammatory response, administration of a single pump-prime dose of methylprednisolone (1 mg/kg) represents the standard of practice in our clinic. The decision to administer methylprednisolone was based on evaluation of the risks and benefits for each patient. Acetylsalicylic acid was discontinued 1 week prior to surgery. After the operation, acetylsalicylic acid (100 mg/day) was resumed within 6-12 h in all patients. Patients were not given NSAIDs postoperatively.

Statistical Analysis

Statistical analysis was conducted using the SPSS for Windows software package (ver. 17; SPSS Inc., Chicago, IL, USA). All variables

were evaluated using visual (histograms, probability plots) and analytical (Kolmogorov-Smirnov test) methods, to determine whether they were normally distributed. Continuous variables are reported as means ± *SDs* for normally distributed variables, and as medians with interquartile ranges for non-normally distributed variables. Categorical variables are presented as numbers and percentages.

Patients were divided into two subgroups according to whether or not they received methylprednisolone. Group comparisons were performed using chi-squared or Fisher's exact tests for qualitative variables, independent *t*-tests for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables. Patients were further categorized into two subgroups according to the presence or absence of PPS; similar analyses were performed for the PPS groups. Logistic regression was used to evaluate associations between PPS and methylprednisolone administration. A p value < 0.05 was taken to indicate statistical significance.

Results

Study Population

A total of 200 patients were included in the study. The clinical characteristics of the methylprednisolone (n = 100; 74 males; mean age = 59.2 ± 11.2 years) and control (n = 100; 68 males; mean age = 59.5 ± 11.1 years) groups are shown in Table I. There was no significant between-group difference in any demographic characteristic.

Effects of Methylprednisolone on PPS Incidence

PPS prevalence was significantly lower in the methylprednisolone group than that of the control group (p = 0.02). Pericardial effusion incidence was significantly lower in patients given methylprednisolone (p = 0.007). There was no between-group difference in the severity of pericardial or pleural effusion. Although statistical significance was not attained, pericardial and pleural effusion were more severe in the control group than in the methylprednisolone group. The efficacy of methylprednisolone for primary prevention of PPS is shown in Table II.

Patients were further categorized into two subgroups according to the presence (n = 59; 37 males; mean age = 58.4 ± 11.8 years) or absence (n = 141; 105 males; mean age = 59.8 ± 10.8 years) of PPS. The clinical characteristics of the patients with or without postpericardiotomy syndrome are presented in Table III. There was no significant between-group difference in the clinical characteristics these subgroups (Table III).

Multivariate Analysis

Logistic regression analysis showed that methylprednisolone (OR = 0.8, 95% CI: 0.25, 0.91, p < 0.026) was independently associated with PPS occurrence after correction for age, male gender and CPB time. The full results of logistic regression analysis are presented in Table IV.

Discussion

Intraoperative methylprednisolone administration was found to be protective against PPS in patients undergoing CABG surgery. More-

Table I. Baseline characteristics of the patients.

	Methylprednisolone group (n = 100)	Control group (n = 100)	*p* value
Age, years, mean ± SD	59.2 ± 11.2	59.5 ± 11.1	0.82
Male, n (%)	74	68	0.35
HT, n (%)	57	60	0.66
DM, n (%)	30	28	0.75
Smoking, n (%)	64	58	0.38
COPD, n (%)	19	24	0.38
Number of anastomoses, mean ± SD	3.4 ± 1.05	3.3 ± 1.06	0.5
CPB time, min, median (IQR)	118 (92.2-141.2)	110 (86-134.7)	0.14
X clamp time, min, median (IQR)	70.5 (55.2-92)	63.5 (53.2-86.7)	0.21

HT: Hypertension; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; CPB: Cardiopulmonary bypass.

Table II. Efficacy of methylprednisolone for the prevention of postpericardiotomy syndrome

	Methylprednisolone (n = 100)	Control (n = 100)	*p* value
PPS, n (%)	22	37	0.02
Postoperative pericardial effusion, n (%)	12	27	0.007
Mild < 10 mm	10	18	0.1
Moderate 10-20 mm	2	5	0.44
Large, > 20 mm	0	2	0.49
Cardiac tamponade, n (%)	0	2	0.9
Pleural effusion, n (%)	13	15	0.68
Below level of diaphragm	6	7	0.77
< 25% of the thorax	5	5	1
> 25% of the thorax	2	3	1

PPS: Postpericardiotomy syndrome.

Table III. Comparison of clinical characteristics in patients with or without postpericardiotomy syndrome.

	Postpericardiotomy syndrome		
	Yes (n=59)	No (n=141)	*p* value
Age, years, mean ± SD	58.4 ± 11.8	59.8 ± 10.8	0.42
Male, n (%)	37 (62.7)	105 (74.5)	0.09
HT, n (%)	29 (49.2)	88 (62.4)	0.08
DM, n (%)	14 (23.7)	45 (31.9)	0.25
Smoking, n (%)	30 (50.8)	92 (65.2)	0.06
COPD, n (%)	12 (20.3)	31 (22)	0.79
Number of anastomoses, mean ± SD	3.19 ± 1.06	3.46 ± 1.05	0.09
CPB time, min, median (IQR)	118 (87-37)	112 (89.5-138)	0.7
X clamp time, min, median (IQR)	63 (47-85)	69 (55.5-91.5)	0.08

HT: Hypertension; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; CPB: Cardiopulmonary bypass

over, the occurrence of pericardial effusion was lower in patients given methylprednisolone. Although not statistically significant, pericardial and pleural effusion were more severe in patients who did not receive methylprednisolone. To the best of our knowledge, this is the first study to assess the protective effect of methylprednisolone against PPS in patients undergoing CABG surgery.

Although the pathogenesis thereof remains to be clearly established, PPS is considered to be immune-mediated inflammatory process triggered by cardiac antigen exposure[7-11]. Myocardial muscle injury during surgery precipitates the release of autoantigens that can trigger host immune responses and the subsequent production of anti-heart antibodies (AHAs) and immune complexes. Engle et al[8] reported that

Table IV. Results of the logistic regression analysis.

	OR	95% CI	*p* value
Age	0.98	0.95-1.01	0.24
Male gender	1.6	0.81-3.1	0.18
CPB time	1.01	0.99-1.02	0.12
Methylprednisolone administration	0.48	0.25-0.91	0.026

OR: Odds ratio; CI: Confidence interval; CPB: Cardiopulmonary bypass.

AHAs were present at high titers in PPS patients. Deschredder et al[12] observed significant correlations between development of PPS and increased immune complexes, and between postoperative AHAs and increased levels of immune complexes, suggesting a possible pathogenic role. Maisch et al[13] further examined specific autoantibody subtypes; in 95% of their PPS patients, antibodies to myocardium and skeletal muscle were detected. Surgery and trauma have been hypothesized as etiologies of the myocardial injury that caused the release of these myocardial antigens. In addition, Snefjella et al[23] demonstrated an increase in pro-inflammatory, and a decrease in anti-inflammatory cytokines upon admission in patients who later developed PPS compared to those who did not. Cardiac surgery with CPB is known to induce a systemic inflammatory response that may further increase the risk of PPS[24,25].

Glucocorticoids are used to treat a wide range of inflammatory and autoimmune diseases. Moreover, randomized trials have demonstrated that perioperative administration of corticosteroids in patients undergoing cardiac surgery with CPB inhibits the production of inflammatory mediators, cytokines, complement, transcription factors and adhesion molecules, and decreases the ratio of proinflammatory to anti-inflammatory interleukins[26].

Although several studies have examined the efficacy of corticosteroids during PPS treatment[16], few have focused on their role in primary prevention of PPS[15,27]. Bunge et al[27] conducted the largest reported trial investigating the potential beneficial effects of high-dose dexamethasone in PPS prevention, and retrospectively analyzed data from 822 PPS patients who underwent valvular surgery. Dexamethasone conferred no protection against PPS or complicated PPS. Mott et al[15] assessed the effects of a prophylactic methylprednisolone regimen on the occurrence and severity of PPS in pediatric patients following cardiac surgery with CPB; methylprednisolone did not reduce the prevalence of PPS. Furthermore, in patients receiving methylprednisolone, the prevalence of complicated PPS was higher. In contrast to these data, we observed a protective effect of methylprednisolone against PPS. This discrepancy is probably due to differences in study design; we evaluated the protective effect of methylprednisolone in adult patients undergoing isolated CABG, which represents a completely different population; immune responses typically differ between adults and children[28]. We also employed strict exclusion criteria.

A limitation of our study was the definition of PPS. No consensus emerged on how to diagnose PPS, which also lacked pathognomonic features. Therefore, comparing results across studies was problematic.

Conclusions

Intraoperative, single-dose methylprednisolone may protect against the development of PPS in patients undergoing CABG. Prevention of PPS can reduce the postoperative morbidity and mortality associated with pericardial effusions after cardiac surgery.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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