

Clemastine to Prevent Adverse Effects of Protamin Sulfate After Coronary Artery Bypass Graft Surgery

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ABSTRACT

Background: Heparin is the only widely used pharmacologic agent for anticoagulation during coronary artery bypass graft surgery (CABG). Failure of adequate and prompt heparin reversal by protamine sulfate can result in hemodynamic instability. Protamine has various side effects. Clemastine as an H1 receptor blocking agent shows positive inotropic effect but not some side effects of non-sedative antihistamines such as cardiac arrhythmia. The aim of this study was to evaluate the effect of clemastine on several hemodynamic responses after protamine sulfate administration in patients subjected to CABG.

Methods: In a prospective randomized controlled trial, 60 patients aged 34-87, with the ASA class II to IV and cardiac ejection fraction $\geq 50\%$ who subjected to elective CABG were enrolled to two equal groups. Patients in group 1 received normal saline (2ml) intravenously as placebo before the operation was completed. Patients in group 2 received clemastine 2 mg (2ml) intravenously at the same time as group 1. After the operation all patients received slowly infusion of protamine sulfate within 7 minutes, through peripheral vein.

Results: Change of MAP in 5 minutes after protamine administration was clinically significant in group 1. No drop in MAP in 5 and 10 minutes after protamine administration was seen in group 2. There was a significant increase in heart rate in 5 and 10 minutes after protamine administration in group 1. There was no significant rise in heart rate before and after protamine administration in group 2.

Conclusion: Clemastine can prevent MAP decrease after protamine administration in patients subjected to coronary artery bypass graft surgery.

Keywords: Clemastine; Protamine Sulfate; CABG; Haemodynamic Stability

INTRODUCTION

Heparin is the only widely used pharmacologic agent for anticoagulation during coronary artery bypass graft surgery (CABG). Its greatest advantage is the ability to be rapidly antagonized by protamine sulfate.

Failure of adequate and prompt heparin reversal by protamine sulfate can result in hemodynamic instability and increased utilization of blood products. Adverse hemodynamic responses to protamine sulfate, such as interference with hemostasis,

anaphylactoid reactions, pulmonary vasoconstriction, and systemic hypotension are reported to occur in 2% of patients^{1,2}.

Systemic hypotension after protamine administration appears to be related primarily to systemic vasodilation mediated by histamine release.³⁻⁵ Histamine characteristically causes dilation of small blood vessels, resulting in flushing, lowered total peripheral resistance, and a fall in systemic blood pressure. In addition, histamine tends to increase capillary permeability.⁶⁻⁹ H1 receptors reside on

endothelial cells, and their stimulation leads to the formation of local vasodilator substances.

Clemastine fumarate, an ethanolamine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative properties. Stimulating H1 receptors has negative inotropic effect. Clemastine shows positive inotropic effect by blocking such receptors. On the other hand it does not have some side effects of non-sedative antihistamines such as cardiac arrhythmia. The intravenous form of clemastine is available, which can be its other advantage. Considering such advantages we choose clemastine as a H1 receptor blocking agent to evaluate its effect on hemodynamic responses after protamine sulfate administration in patients subjected to coronary artery bypass graft (CABG) surgery.

PATIENTS AND METHODS

In a prospective randomized controlled trial done between 1st march 2003 and 15th February 2004, we enrolled 70 patients aged 34-87, with the ASA class II to IV and cardiac ejection fraction equal or greater than 50% ($EF \geq 50\%$) who subjected to elective CABG to two equal groups. The sample size (60 patients) was calculated by statistician considering $\alpha=0.05$. Of the 70 enrolled patients 10 were excluded because of incomplete data. Group 1 consisted of 30 patients who received normal saline (2ml) intravenously as placebo 5 minutes before the cardiopulmonary bypass (CPB) was completed. And group 2 consisted of 30 matched patients who received clemastine 2 mg (2ml) intravenously at the same time as group 1. The medication and the placebo were prepared by a technician who was blind to gathering the data and also to interpreting the results. The data were gathered during the one-year period in a specific notebook by two technicians who were blind to the patients' allocation and drug infusion.

The anesthesiologist as well as those who interpreted the results were blinded to the patients' allocations. The operations were held in two teaching hospitals (Nemazi and Faghihi hospitals) affiliated to Shiraz University of Medical Sciences, Shiraz, South of Iran. The research was approved by vice chancellor for research in Shiraz University of Medical Sciences.

Before the operation an arterial catheter via

left radial artery and an internal jugular vein cannula were inserted to monitor the mean arterial pressure (MAP) and central venous pressure (CVP). After the CPB all 60 patients received slow infusion of protamine sulfate (protamine to heparin ratio 1.5/1) within 7 minutes, through a peripheral vein. Heart rate (HR), MAP, and CVP were monitored before and after 5, 10, and 30 minutes of protamine administration in both groups. Changes in the preceding parameters were considered clinically significant if the increase or decrease were more than 10% of the baseline. Statistical analysis was performed using the SPSS software version 11. T-test was used to compare the parameters between the groups and $P < 0.05$ was considered significant.

RESULTS

MAP before and 5, 10, and 30 minutes after protamine administration were 104.73 ± 9.43 mmHg, 92 ± 10.3 mmHg, 94.6 ± 11.7 mmHg, and 100.26 ± 10.43 mmHg in group 1, which shows a significant drop in MAP in 5 and 10 minutes after protamine administration. Change of MAP in 5 minutes after protamine administration was clinically significant because the change was more than 10% of the baseline.

MAP in group 2, before and 5, 10, and 30 minutes after protamine administration were 108 ± 11.74 mmHg, 107.2 ± 11.6 mmHg, 107.56 ± 10.82 mmHg, and 110.3 ± 10.79 mmHg. No drop in MAP in 5 and 10 minutes after protamine administration was seen (table 1). Mean difference of MAP between 2 groups in 5 minutes after protamine infusion was 11, which was more than 10% of baseline and was clinically significant.

There was a significant increase in heart rate in 5 and 10 minutes after protamine administration in group 1 (table 2) but only the change in 5 minutes was clinically significant. In group 2, there was not clinically significant changes in HR in 5 minutes after protamine administration, which means that clemastine had beneficial effect on heart rate by inhibiting its rise. There was no significant rise in the heart rate after protamine administration in group 2 compared with before protamine administration.

The difference between mean of the heart

rate between the two groups after 30 minutes after protamine administration was not statistically significant ($p=0.122$).

Table 1: The comparison of mean arterial pressure (MAP) before and 5, 10, and 30 minutes after protamine administration between the groups.

Time (Minutes)	MAP±SD		P-value
	Group 1	Group 2	
Baseline	104.73±9.43	108.03±11.74	0.14
5	92±10.3	107.2±11.6	<001
10	94.6±11.7	107.56±10.82	<001
30	100.26±10.43	110.3±10.79	<001

MAP±SD=Mean arterial pressure± standard deviation

Table 3 shows the central venous pressure before and after 5, 10, and 30 minutes of protamine administration in both groups. There was a significant drop in CVP after 5, and 10 minutes of protamine administration in group 1. But the CVP in group 2 did not change significantly. Changes of CVPs after protamine administration between the groups were statistically but not clinically significant.

Table 2: The comparison of heart rates before and 5, 10, and 30 minutes after protamine administration between the groups.

Time (Minutes)	Mean HR±SD		p-value
	Group 1	Group 2	
Baseline	92.1±9.46	94±10.99	0.23
5	104.1±8.67	94.93±10.1	<001
10	101.43±8.66	95.23±11.58	<001
30	96.53±10.78	93.66±11.74	not significant

HR = Heart rate, SD = standard deviation

DISCUSSION

Management of patients undergoing CABG

Table 3: The comparison of CVP before and 5, 10, and 30 minutes after protamine administration between the groups.

Time (Minutes)	Mean CVP±SD		p-value
	Group 1	Group 2	
Baseline	10.73±1.22	11.1±1.82	0.36
5	8.56±1.54	10.6±1.69	<001
10	9.06±1.57	10.9±1.7	<001
30	10.33±1.56	11.53±1.50	0.004

CVP= Central venous pressure, SD = standard deviation

is one of the important tasks of cardiac anesthesiologists. Heparin is the only widely available pharmacologic agent for anticoagulation during cardiopulmonary bypass (CPB). Its greatest advantage is its ability to be rapidly antagonized by protamine. Lots of trials have been done to investigate the protamine induced hemodynamic instability,^{2,10} some others to figure out the mechanism of such instability.^(9,11) Adverse reactions to protamine are less than 2% in the USA.¹² Higher reported incidences are because of different practice patterns, differing patient populations, and lack of uniform definition of protamine reaction.

There are various forms of protamine-induced hemodynamic instability. Systemic hypotension is one of the most important ones. It can be caused by systemic vasodilation rather than impaired myocardial contractility.¹² Systemic vasodilation can be a result of H1 receptors stimulation, which will tend to histamine release. Histamine can affect vascular smooth muscles and relax the small blood vessels. The effect that is proposed to be done through NO production.¹³

The other adverse effect of protamine is pulmonary vasoconstriction, which can increase pulmonary artery pressure. And in some cases can cause acute dysfunction of right ventricle, which will lead to severe hypotension.¹⁴ Anaphylactoid reaction is the other protamine related complication, which will lead to systemic hypotension, increased vascular permeability, and cardiovascular collapse.¹⁵ To avoid untoward side-effects, many trials have been done to examine the alternative drugs for protamine. Some of these alternatives such as heparinase and PF4 are under investigations and have not replaced protamine yet.⁽¹⁶⁾ Some studies revealed that diluted, small intermittent doses of protamine infused very slowly via peripheral vein, can reduce hemodynamic instability. H1 receptors have higher affinity for histamine release than H2 receptors. The response to stimulation of H1 receptors is rapid onset but short lived. H2 receptors by contrast are slow reacting but sustained.³

Parson et al in 1989 studied the effects of histaminereceptor blockade on hemodynamic responses to protamine. They studied cimetidine and

chlorpheniramine (H2 antagonists) and concluded that hemodynamic changes were only partially mediated by histamine action, normal response to protamine may be modified, but not abolished by H1 and H2 receptor blockade. They finally concluded that this blockade might however, prevent the reduction in right heart preload and increase in heart rate.⁵ In 1990 Kambam et al studied the prophylactic administration of diphenhydramine (H1 blocker) and cimetidine in prevention of protamine-related hemodynamic effect. They concluded that prophylactic administration of histamine receptor blockers prevented some of adverse hemodynamic effects associated with protamine administration.³

Famotidine (H2 antagonist) and diphenhydramine were used by Mayumi et al in 1992 to ameliorate protamine-induced hypotension in open heart surgery.¹⁷ The results strongly suggested that famotidine was beneficial in reducing protamine-induced hypotension after CPB, while diphenhydramine had not the same effect.¹⁷

Our results were in accordance with the study done in the year 2000 in Poland. In that study the researchers examined clemastine to accelerate the normalization of arterial blood pressure after protamine administration.¹⁸ They concluded that administration of clemastine before CPB could reduce peripheral vasodilation and capillary leak and it could cause a faster increase in arterial blood pressure toward a physiologic range.

In conclusion we found that clemastine could prevent MAP decrease after protamine administration in patients subjected to coronary artery bypass graft surgery. But it did not have any clinically significant effect on heart rate or CVP. Considering the results of this study and less side effects and availability of intravenous form of clemastine, it may be a suitable drug to prevent adverse effects of protamine administration in patients subjected to CABG.

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