



Heparin Resistance During and Post-Intravenous Nitroglycerin Infusion

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Abstract

Nitroglycerin has been reported to reduce activated partial thromboplastin time (aPTT) values in patients treated with concurrent heparin and nitroglycerin. However, studies have yielded conflicting results. To determine whether intravenous nitroglycerin alters the anticoagulant effect of heparin, we prospectively evaluated twenty patients admitted for coronary angioplasty by measuring their aPTT both before initiation and after addition of nitroglycerin to heparin therapy. The results showed that the mean of aPTT at the baseline when patients were on heparin alone was not significantly different from aPTT measured upon addition of nitroglycerin, and 30 min following the cessation of nitroglycerin infusion, when patients were still on the same dose of heparin. Therefore, no direct effect of nitroglycerin on the anticoagulant effect of heparin was observed in this study.

Keywords: Heparin; Nitroglycerin; Resistance.

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1. Introduction

Atherosclerotic coronary heart disease continues to be one of the leading causes of death [1]. Since the infarct size is a strong prognostic indicator of morbidity and mortality, it is imperative that therapy be immediately directed towards the limitation of the infarct size [2].

Increasing awareness of the pathophysiologic role of abnormal coronary vasomotor tone, plaque ulceration and coronary

thrombosis in acute ischemic coronary syndrome has led to the increased use of intravenous heparin in the management of these patients. A significant proportion of patients appear to benefit from intravenous nitroglycerin, therefore, unless there are contraindications to its administration (such as systolic blood pressure <100 mmHg or cardiogenic shock) administration of intravenous nitroglycerin for a period of 24 to 72 h is recommended. This therapeutic combination is mainly being used in the cardiac catheterization laboratory and the critical care unit, particularly in patients undergoing percutaneous coronary angioplasty, in an attempt to reduce the risk of acute

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coronary occlusion [3]. However, reports since 1985, suggesting that intravenous nitroglycerin may induce resistance to anticoagulant effects of intravenous heparin is a cause for concern [4-6].

Several studies have attempted to reveal the answer to this question that what is the reason that intravenous nitroglycerin prolongs partial thromboplastin time (aPTT) during co-administration with heparin?

The implication is that higher doses of heparin may be needed in patients treated with nitroglycerin and if the dose of nitroglycerin is reduced or discontinued, excessive anti-coagulation and hemorrhage may occur [7].

Since the exact mechanism which may be responsible for the effect of nitroglycerin on heparin requirement has not been established, we prospectively closely monitored the aPTT in a group of Iranian patients following angioplasty.

2. Materials and methods

Patients who were candidate for coronary angioplasty, and were admitted to Shariati Medical Center during fall and winter 2003, were the group of our study. They were also designated to receive both continuous intravenous infusion of heparin and nitroglycerin. Patients were excluded from the study if they were hemodynamically unstable, had received warfarin before or during hospitalization, had significant renal dysfunction (serum creatinine >3 mg/dL) or had clinical or laboratory evidence of liver dysfunction. Twenty patients (12 male and 8 female) complied with these criteria and were included in this study.

All patients were on constant therapeutic dose of intravenous heparin (700-1200 U/h) for at least 6 h prior to the inclusion in this study. The use of aPTT as an indicator of heparin-induced anticoagulation effect is generally accepted, and its use is supported by reports of a 1.5-2 fold decrease in recurrence

of venous thromboembolic disease when heparin is used to prolong aPTT.

Baseline aPTT was obtained prior to the initiation of nitroglycerin infusion. On the same dose of heparin, the nitroglycerin infusion rate was gradually increased from 5 mg/min to a maximum of 67-300 mg/min according to the patient's systolic blood pressure. Nitroglycerin infusion rate increment was stopped if a patient experienced a 10% drop in systolic blood pressure. This was achieved within one hour and the patients were maintained on this constant drip of nitroglycerin for additional 30 min. aPTT was measured again at the peak of nitroglycerin infusion rate. Nitroglycerin was then tapered down over 15 min. Another blood sample was drawn at this time to determine aPTT. These blood samples were collected in tubes containing 0.5 ml of 3.8% sodium citrate, placed immediately on ice and centrifuged at 3200 rpm, for 5 min to obtain platelet poor plasma. All determinations of aPTT were made within 2 hours of blood sampling.

This protocol was reviewed and approved by The Review Board for Human and Animal Studies of Tehran University of Medical Sciences.

Analysis of variance for multiple variables performed to assess the statistical significance of difference in aPTT measured prior to the addition of nitroglycerin, at the peak of nitroglycerin infusion rate and following discontinuing nitroglycerin infusion. A *p* value of 0.05 was considered statistically significant.

3. Results

Demographic characteristics of patients included in this study are presented in Table 1. Table 2 shows the mean of aPTT of patients that were measured at three separate times, when patients were receiving heparin alone (baseline), during concomitant administration of heparin and nitroglycerin at the maximum

Table 1. Demographic characteristic of patients.

Characteristics	Male	Female
Number of patients	12	8
Age (mean \pm SD)	59.10 \pm 11.61	62.9 \pm 9.98

nitroglycerin infusion rate, and finally after discontinuing nitroglycerin infusion when the patients were continuing to receive just heparin.

The aPTT at the baseline when patients were on heparin alone (92.75 \pm 16.65 Sec) was not significantly different from aPTT measured upon the addition of nitroglycerin (94.40 \pm 17.58 Sec), and aPPT determined 30 min following the cessation of nitroglycerin infusion, while patients remained on the same dose of heparin (95.20 \pm 19.39 Sec; $p=0.61$).

4. Discussion

An inhibitory effect of nitroglycerin on the anticoagulant effect of heparin was first suspected based on clinical observations. One study showed a blunted response to a bolus injection of heparin when administered concurrently with nitroglycerin. Other studies showed fluctuations of aPTT in patients receiving continuous heparin infusion directly coinciding with intravenous nitroglycerin administration [4, 5]. Another study found an increase in heparin requirements and a decrease in aPTT in a few numbers of patients who received nitroglycerin doses of 350 mg/min [6].

In contrast, other studies have found no difference in the aPTT prolongation produced by heparin with or without concurrent, short-term (1-2 h) nitroglycerin intravenous infusion [7]. Nottestad and his colleagues have reported no difference in heparin dosage requirement between 15 cardiac patients receiving no nitroglycerin and 9 patients receiving 20-150 mg/min of nitroglycerin [8]. Similar to the

findings of Pye et al. [7] and Nottestad et al. [8], we found no evidence of significant nitroglycerin-induced heparin resistance as measured by alterations in aPTT in patients who received both drugs concurrently in a clinically relevant setting using therapeutically effective doses of heparin and nitroglycerin.

In this study each patient also served as his or her own control of aPTT, since we measured aPTT prior to the initiating of nitroglycerin infusion, at the peak of hemodynamic effects of concomitant nitroglycerin and also after discontinuing nitroglycerin infusion. It should be contemplated that differences in the propylene content of the nitroglycerin formulation are unlikely to account for the difference in reported results since heparin effect is not modified by the presence or absence of propylene glycol [4, 9, 10].

The role of intravenous heparin is to improve infarct-artery patency. It seems that adjuvant intravenous heparin is most beneficial when the degree of prolongation of aPTT value are >1.5 times of control and inversely correlates with the incidence of reocclusion [5]. At the same time intravenous nitrates improve myocardial ischemia primarily by affecting pre-load and after-load, which can reduce oxygen requirements, myocardial wall stress, and expansion of the infarcted region, resulting in long-term improvement in clinical outcome. Therefore it is not unexpected that heparin combined with nitroglycerin infusion, would show a significant additive benefit compared with each agent alone [11-13].

Table 2. Activated partial thromboplastin time (aPTT) in patients received heparin and nitroglycerin.

Therapeutic Regimen	Mean	SD	SE
Heparin alone	92.75	16.65	3.72
Heparin + Nitroglycerin	94.40	17.58	3.93
Heparin (Nitroglycerin stopped)	95.20	19.39	4.33

5. Conclusion

Findings of this study suggest that intravenous nitroglycerin can be safely administered to the patients receiving heparin. In usual dosages, it is unlikely that nitroglycerine interact with heparin leading to change in heparin's anticoagulant effect, measured by aPTT. However, it is important to be aware of a potential impairment of anticoagulation that seems to occur with nitroglycerin. Therefore, frequent and early monitoring of aPTT is advised when intravenous infusion of two drugs is used at the same time.

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