Does Intraoperative Nitroglycerin Infusion have an Effect on Heparin Anticoagulation and AT Activity?

İNTRA OPERATİF NİTROGLİSERİN İNFÜZYONU HEPARIN ANTİKOAGÜLASYONUNU VE AT III AKTİVİTESİNİ ETKİLER Mİ?

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Summary

The effects of nitroglycerin infusion on heparin anticoagulation and antitrombin III activity were evaluated in twenty adult patients undergoing coronary artery bypass surgery. 10 patients in the study group received intraoperative nitroglycerin infusion at a rate of I fig/ kg/nun. 10 patients in the control group received no intraoperative nitrates. Heparin 300 units/kg was administered to all patients. The activated partial tromboplastin time (aPTT), prothrombin time (FT), thrombin time (TT), plasma fibrinogen level and AT HI activity were measured after induction, 5 minutes after heparin administration, 30. minutes at the cardiopulmonary bypass, 5 minutes after protamine administration and at the end of the surgery. Heparin sensitivity, total heparin requirement and heparin consumption were also calculated. There were no significant differences in aPTT.TT. fibrinogen levels and AT III activity between the groups at any time period. We concluded that a modest dose of intravenous nitroglycerin infusion does not interfere with the anticoagulant effect of heparin in patients undergoing coronary artery bypass surgery.

Key Words: Drugs: Nitroglycerin infusion, Heparin, Coagulation: AT TIT activity, aPTT, PT, TT, Fibrinogen,

Anaesthesia: Coronary artery bypass surgery

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Özet

Koroner arter cerrahisi uygulanan 20 hastada nitrogliserin infüzyonıtnın heparirı antikoagülasyonuua ve AT III aktivitesine etkisi araştırılmıştır. Çalışma grubundaki 10 hastaya iıtraoperatif I flg/kg/min dozunda nitrogliserin infüzyonu uygulandı. Kontrol grubundaki 10 hastaya ise nitrogliserin infiizyonu uygulanmadı. Bütün hastalara heparin 300 U/kg verildi. Aktive edilmiş parsiyel tromboplustin zamanı (aPTT), protrombin zamanı (PI), trombin zamanı (TT), plazma fibrinojen seviyesi ve AT III aktivitesi indüksiyondan sonra, heparin uygulamasından 5 dk sonra, kardiopıılmouer bypass 'ın 30 dk - da, protaınin uygulamasından 5 dk sonra ve operasyonun sonunda ölçüldü. Heparin sensitivitesi, total heparin gereksinilin ve heparin tüketimi de hesaplandı. Ölçüm zamanlarında gruplar arasında aPTT, PT, fibrinojen seviyesi ve AT IJI aktivitesinde anlamlı farklılık saptanmadı. Koroner arter cerrahisi uygulanan hastalarda orta dozda intravenöz nitrogliserin uygulamasının heparinin antikoagülan etkisini etkilemediği kanısına varıldı.

Anahtar Kelimeler: İlaç: Nitrogliserin infüzyonıı, Koagülasyon: AT III aktivitesi, aPTT, PT, TT, Fibrinojen, Anestezi: Koroner arter cerrahisi

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Although the basic reason for the wide variability in the individual anticoagulant response to heparin is poorly understood, iv nitroglycerin (NTG) infusion has been implicated as one of the reasons in resistance-to heparin (1). While several mechanisms including an acceleration in heparin degradation and a NTG-induced qualitative ATITI abnormalities were suggested to be responsible, there are several studies failed to identify a nitroglycerin-induced heparin resistance (2-4).

We investigated the influencv, f a modest dose of NTG infusion used intraoperatively on the anticoagulant effect of heparin and on AT IJI activity in patients undergoing coronary artery bypass graft (CABG) surgery

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Methods

Twenty adult patients undergoing elective CABG were studied. The study protocol was approved by the Ethics Committee and each patient gave informed consent. Patients with ventricular aneurysm with thrombus infection, congenital AT III deficiency and patients receiving oral contraceptives, autologous blood, heparin or NTG treatment preoperatively were excluded from the study. Routine medication was maintained even at the morning of operation in all patients.

Patients were premedicated with diazepam 10 mg. orally in the evening before the surgery and one hour before the induction of anaesthesia. Anaesthesia was induced with etomidate, fentanyl and vecuronium bromide and maintained with isoflurane, 02-N20 and supplemented fentanyl. Twenty patients were allocated randomly to two groups. Patients in Group I (n=10) acted as control group. Ten patients in group II received NTG infusion at a rate of l(J-g/ kg/min after the induction of anaesthesia until the end of the cardiopulmonary bypass (CPB). In all of the patients, heparinization was obtained by an initial dose of heparin sulfate 300 units/kg into the right atrium before cannula*-tion and it was monitored by ACT value (Hemochron 801) kept greater than 400 second throughout CPB. At the end of the CPB, residual circulating heparin was neutralized by protamine hydrochloride (according to ACT, Protamine Dose Assay Worksheet, Hemochron 801). The activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT), plasma fibrinogen level and AT III activity were measured blindly for five times; after the induction (tl), 5 min after heparin administration (12), at 30th min of CPB (t3), 5 min after protamine administration (t4), and at the end of the surgery (t5) .

The blood samples were collected in plastic lubes with sodium citrate (4.5 ml blood, 0.5 ml 0.13 mmol/lt, Tri-Na citrate 9NC73.8 %0.5 ml). Plasma separation was then performed within 1 hour after blood collection to measure aPTT, PT, TT, fibrinogen (clotting assay, STA Compact System.- Diagnostica STAGO FRENCH) and AT III activity. ATIH activity was measured quantitatively by the synthetic chromogenic substrate method (Stachrom Antilhrombin-III).

Sensitivity to the initial dose of heparin [Postheparin ACT(s) - Baseline ACT(s)/Initial dose of heparin (1U)], the total (X) intraoperative heparin requirement [X of heparin during operation (IUyWeight of patient (kg)] and heparin consumption [Total heparin requirement (IU/kg) / Duration of CPB (min)] were calculated (5).

Data were expressed as the mean ± standard error. Comparison of two means performed using the Student's t test and comparison of several means was performed using repeated measure of variance analysis (ANOVA). p values less than 0.05 was considered as statistically significant.

Results

Clinical characteristics of the patients were not different between the two groups (Table 1). Although sensivity to the initial dose of heparin was lower in NTG group than the control group (1.56±0.13 and 1.42±0.10 group I and II respectively), the differences were not statistically significant. Neither heparin requirements nor heparin consumption (5.69±0.01 and 4.60±0.0 iu/kg/min in group I and 11 respectively) found to be significantly different between the two groups (Table 2). Total heparin requirements and protamine doses were similar in the two groups and they were not affected by the modest dose of NTG infusion.

No significant differences were observed in aPTT, PT, TT, fibrinojen levels between the two groups (Table 3).

AT III activity decreased after the heparin administration (69.08±8.98 % in group 1 and 72.07±8.77 % in group II) and found significantly lower ($p<0.05$) during the CPB (55.01±8.82 % and 48.27±6.63 % in group I and II respectively) and after protamine administration (46.64±6.64 % in

Table 1. Clinical characteristics of the patients. (Mean ± SEM)

	Group I	Group II
Sex (M/F)	8/2	7/3
Age (years)	57.11±3.57	53.11=l=1.98
Weight (kg)	71.78±2.86	76.33il.74
Clamp Duration (min)	38.33±4.41	43.89±5.39
CPB duration (min)	66.67--L-7.27	74.22±6.98

Table 2. Distribution of heparin sensitivity, heparin requirement, heparin consumption and total heparin and protami-n dose's according to the groups (Mean ± SEM)

	Group I	Group II
Heparin sensitivity	1.56*0.13	1.42±().l()
Heparin requirement (IU/kg)	344.37il0.19	3 18.1 ±0.09
Heparin consumption (lU/kg/min)	5.69±0.0I	4.60±0.0()
Total heparin doses (nig)	245.56il4.2S	240.56±5.80
Total protamin doses (nig)	225.00± 14.43	236.11±6.05

Table 3. Activated partial thromboplastin time (aPTT), Prothrombin time (PT), Thrombin time (TT) and fibrinogen levels of the patients (Mcan±SEM).tl : after induction, t 2:5 min after heparin administration, t 3: at 30 min of CPB, t 4: 5 min after protamine administration, t 5: at the end of the operation.

		t1	t2	t3	t4	t5
al'TT	Group 1	44.U6.0	>240	>240	65.416.9	37.612.9
(sec)	Group II	45.4±3.8	234.4±5.6	>240	63.318.9	53.418.3
I'l	Group 1	13.6±0.5	67.7116.6	66.6116.9	20.911.4	17.610.8
(sec)	Group II	13.5±0.5	88.5±15.8	88.6115.8	22.613.47	17.612.0
IT	Group 1	18.5+.0.7	>60	>60	23.810.8	21.6+0.4
(sec)	Group II	19.4±0.8	>60	>60	24.511.1	20.010.7
Fibrinogen	Group 1	200.3±21.2	188.7117.1	•144.1113.6	158.7113.6	184.217.6
(mg/dl)	Group II	194.6±17.7	176.1117.8	110+12.5	136.9124.0	192.0129.3

group I and 45.53±7.73 % in group II) in both groups. At the end of the operation ATI 11 activity remained lower than the baseline in both groups (63.78±8.20 % and 61.03±6.05 % in group I and II respectively).Although AT III activity decreased more in group II, no significant difference was observed between the two groups (Figure I).

No excessive hemorrhage was observed following cessation of NTG after CPB.

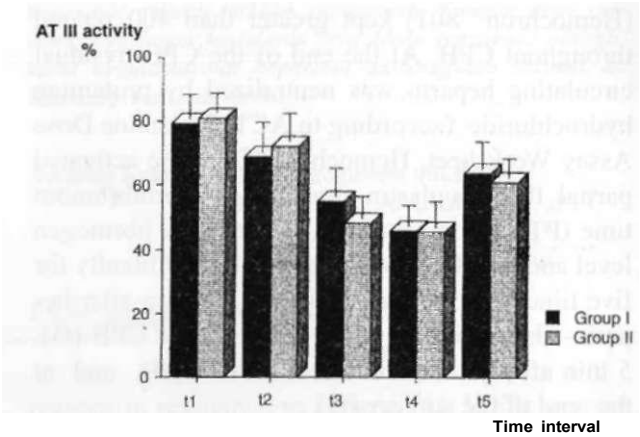

Figure 1. AT i11 activity of the patients, i1 : A11er induction, i2: 5 min after heparin administration, t3: at 30th min in CPI3. l4: 5 min after protamine administration, t5: at the end of the operation.

Discussion

Inadequate heparinization during CPB can result in complications that range from subtle disturbances in the coagulation cascade to severe coagulopathy. The clinical consequences include; excessive postoperative bleeding, intravascular coagulation and even thrombosis of the extracorporeal circuit (5,6).

Previous reports have raised the possibility that the iv NTG therapies frequently employed in patients with unstable angina pectoris may contribute to the development of heparin resistance (1,2,7-9). Marciciak and Gockerman reported that preoperative heparin and NTG therapy are associated with a decreased ACT response to intraoperative heparin

and this depletes plasma AT III levels and this depletion reduces the effectiveness of subsequently administered heparin (10). But the effects of intraoperative NTG infusion on heparin anticoagulation are still controversial. (11-14). These reports on heparin resistance have been based on small populations. According to the limited number of communications in the literature, heparin resistance during CPB is a distinct clinical entity but the available documentation is inadequate with inconsistent data, the problem has been poorly defined.

An NTG induced heparin resistance may be explained by various mechanisms; direct interaction on a molecular basis, formation of an NTG-plasma protein complex inactivating negatively charged heparin like protamin, depletion of coagulation inhibitors, influence on heparin elimination or metabolism by NTG (14).

An inhibitory effect of nitroglycerin on the anticoagulant effect of heparin was first suspected based on clinical observations (2,7). While Col et al (7) reported that a decreasing clotting time associated with increasing NTG concentrations, Habbab and Haft (2) observed that nitroglycerin induced heparin resistance occurcd in patients given preparations both with and without propylene glycol, thereby suggesting a direct nitroglycerin effect. They indicated that an increase in the infusion rate of NTG causes a decrease in aPTT in spite of a constant heparin infusion rate. Conversely, slowing the NTG infusion led to an increase in aPTT (2,15). However, their results were not analysed statistically and the study had no control group.

In some of the studies, it was reported that intravenous nitroglycerin induced heparin resistance occurs at a critical nitroglycerin dose and suggested that a nitroglycerin induced qualitative ATIII abnormality may be the underlying mechanism (1). However, others observed that NTG can interfere with the anticoagulant effect of heparin even at low doses, and suggested that it was likely to be a result of a reduction in plasma heparin levels, perhaps through accelaralion of normal heparin elimination (7,8). They suggested that early and frequent monitoring may therefore be appropriate when intravenous nitrates and heparin arc used in combination (4,7,8,16).

Conversely, in the other studies it was reported that iv NTG infusion do not interfere with the anticoagulant effect of heparin in healthy volunteers or in modest doses or in patients during short tciTrj administration or in vitro studies (11.12,14,16,17). Reich et al (12) reported that a modest dose of iv NTG infusion do not interfere with the anticoagulant effect of heparin in patients undergoing elective myocardial revascularization or single valve replacement surgery.

In our study, AT III activity decreased significantly after heparin administration and remained significantly lower even at the end of the operation in both groups. Although sensitivity to the initial dose of heparin was lower and AT III activity decreased more in NTG group than the control group, no statistically significant difference was found between the two groups. Our results indicate that clinically relavant dose of NTG had no inhibitory effect on the anticoagulant effect of heparin requirements and consumptions between two groups. The study design was limited on small population and higher doses of NTG were not administered because of significant hypotension. Whether high-dose or longer term infusion would produce different results remains unknown.

In conclusion, the modest doses of NTG infusion (1 fig/kg/min) do not interfere with the anticoagulant effect of heparin and ATlI1 activity in patients undergoing CABG surgery. The potential for NTG induced heparin resistance at higher doses needs further investigation.

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