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Intracatheter nitroglycerin infusion fails to prevent catheter-related venous thrombosis: a randomized, controlled trial

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Abstract *Objective*: Catheter-related thrombosis is a common problem in the pediatric intensive care unit. Strategies that reduce the incidence of thrombosis may have significant clinical advantage. Nitroglycerin (NTG) infusions release nitric oxide (NO). NO is responsible for much of the vasodilating and antithrombotic properties of the vasculature. We hypothesized that an intracatheter NTG infusion would reduce the incidence of catheter-related thrombosis.
Design: Prospective, randomized, controlled trial.
Setting: Pediatric intensive care unit.
Patients and participants: Children of 6 years or less with femoral venous catheters who were not on antithrombotic therapy.
Interventions: Subjects were randomly assigned to NTG or control groups. NTG group patients received NTG at 0.1 mcg · kg · min in 5 % dextrose; control group patients received only 5 % dextrose. Infusions were delivered continuously through the catheter until the catheter was removed. Demographic data, physical and laboratory findings, catheter insertion attempts and infusate composition were recorded. Clinical evidence of vascular thrombosis or catheter malfunction was noted. Ultrasound examinations were performed within 2 days of catheter insertion and within 2 days after removal.
Measurements and results: Forty-four patients (age 12.0 ± 2.6 months) completed the study, 21 in the NTG group and 23 in the control group. Duration of catheter placement was 7.5 ± 0.7 days. Twelve of 44 patients (27 %) had thrombi: 7/21 in the NTG group; 5/23 in the control group (p = NS). There were no significant differences between children with and without thrombi in age, gender, number of insertion attempts, duration of catheter placement, clinical signs of thrombosis or infections.
Conclusions: Catheter-related thrombosis is common after placement of femoral venous catheters in children. Low dose intracatheter NTG infusion does not protect against catheter-related venous thrombosis in children.

Key words Catheter-related thrombosis · Central venous catheter · Children · Venous thrombosis · Nitroglycerin · Nitric oxide

Introduction

Vascular thrombosis is a major complication associated with the use of central venous catheters [1, 2, 3]. Factors associated with the initiation and propagation of thrombosis include endothelial damage during catheter insertion, blood vessel occlusion, low flow states, turbulent flow, patient and infusate characteristics and catheter composition [1, 4, 5, 6]. Successful inhibition of catheter-related thrombosis would substantially re-

duce the incidence of the complications associated with this.

Nitroglycerin (NTG) has been utilized primarily as a venodilator for over 100 years. NTG stimulates guanylate cyclase, presumably through the generation of nitric oxide (NO) [7], a molecule that has a significant role in maintaining the vasodilating and antithrombogenic properties of normal vasculature [7, 8, 9, 10, 11, 12]. Administration of NTG protects against endotoxin-induced glomerular thrombosis in rats [13], reduces platelet adhesion to mechanically injured vascular endothelium [14] and disrupts platelet aggregates in the retina of humans [15]. High doses of NTG are well tolerated in humans for several days [16]. Because of these antithrombotic and venodilating properties, we hypothesized that intracatheter infusion of NTG would protect against femoral venous catheter-related vascular thrombosis in children.

Materials and methods

Study population and data collection

Children from birth to 6 years of age, hospitalized in the pediatric intensive care unit, in whom the critical care team had elected to place a double or triple lumen femoral venous catheter were eligible for the study. Patients were excluded from the study if they were receiving nitrovasodilators, phosphodiesterase inhibitors, heparin or warfarin. In addition, patients with thrombocytosis (platelets > 1,000,000) or a history of previous femoral venous catheter placement were excluded from study. After written informed consent had been obtained, subjects were randomized to a NTG group (intracatheter NTG infusion) or a control group (intracatheter 5% dextrose in water infusion). Randomization took place in the pharmacy utilizing a sealed envelope method. NTG or control solutions were coded by patient number and labeled as *catheter thrombosis study infusion* and delivered to the patient's bedside. Other than the pharmacist, no member of the health care team or family was aware of an individual subject's group assignment. The study was conducted according to the principles established in Helsinki for the treatment of human subjects.

Subjects in the control group received a solution containing only 5% dextrose in water, while patients in the NTG group received an infusion of NTG at 0.1 mcg · kg · min in 5% dextrose in water carrier. In selecting the dose of 0.1 mcg·kg·min for the study, we attempted to choose a dose small enough to have insignificant hemodynamic effects (< 0.25 mcg · kg · min) while great enough to have anti-platelet effects. Previous studies indicate that customary NTG infusion doses achieve plasma concentrations known to inhibit platelet aggregation [17, 18, 19].

Infusions were delivered through the most proximal lumen of the multi-lumen catheter in order to provide maximal exposure of the catheter surface and surrounding vessel wall to high infusate concentrations. Whenever possible, no additional solutions were administered through this lumen. The investigational pharmacists were responsible for determining the individual patient's concentration of NTG in solution necessary to insure that this NTG dose was delivered at a rate of 1 ml/h. Study drug infusions were continued uninterrupted for the duration of the study with the exception of transient discontinuation as new drug arrived from the pharmacy. The study ended when the central venous catheter was removed from the patient. Data consisting of patient demographics, diagnosis, history, physical and laboratory findings, catheter characteristics, date of catheter placement, composition of catheter infusates (total parenteral nutrition (TPN), heparin, intralipid) and number of attempts/difficulties with catheter insertion were recorded. Number of placement attempts was defined as the number of needle penetrations into the skin required in obtaining vascular access.

Clinical markers of vascular thrombosis were recorded daily. These markers included extremity edema, extremity color change or catheter insertion site redness or exudate, and mechanical problems with catheter occlusion. Edema was quantified using daily mid-thigh diameter measurements. Skin color was noted as normal, erythematous, cyanotic or mottled. Exudate included any serous, sanguinous or purulent discharge from the catheter insertion site. Bedside nursing staff were queried regarding problems with flushing or drawing back from the catheter. Positive blood cultures from the catheter were recorded and catheter-related infections were defined as follows. *Catheter site inflammation* – presence of lymphangitis, purulence or at least two of the following: erythema, tenderness and/or increased warmth. *Catheter site infection* – catheter site inflammation along with a positive site culture. *Catheter-associated infection* – the study utilized the CDC definition for laboratory-confirmed bloodstream infection for primary bacteremia and clinical sepsis [20].

Ultrasound examinations

Ultrasound is used to diagnose venous thrombosis and is currently the primary screening tool for this complication in many institutions in the United States [21, 22, 23, 24, 25]. Ultrasound examinations of the catheterized femoral vein were performed and analyzed by the radiology investigator within 2 days of catheter insertion and then no more than 2 days following catheter removal. Gray scale images were obtained to evaluate for thrombosis, defined as intravascular echogenic material observed in two planes and attached to the vessel wall or catheter. Vascular thrombosis was defined by gray scale ultrasound visualization of a thrombus (echogenic filling defect within the vessel lumen) and/or absence of a Doppler signal [21, 26]. The ultrasound examination included visualization from the catheter entry point into the femoral vein cephalad to the tip in the external iliac vein or inferior vena cava. This was correlated with radiographic determination of catheter tip location. Color Doppler ultrasound examination was used to evaluate flow in the femoral and iliac veins and the inferior vena cava. The use of color Doppler imaging provided information regarding flow characteristics including velocity, direction, quality (laminar or turbulent), as well as detection of flow in small collateral vessels [27, 28]. The results of the ultrasound examinations were made available to the primary care team who were responsible for any further management decisions. Ultrasound examinations were performed with an Acuson 128 (Acuson, Mountain View, Calif.) unit with 5.0 and 10.0-MHz sector transducers capable of allowing color Doppler ultrasound evaluation.

Patients who died prior to completion of the study did not receive a final ultrasound study. Data regarding the presence or absence of venous thrombosis were obtained in these patients at the time of autopsy. Patients who did not complete a second ultrasound study or autopsy after catheter removal were excluded from the final analysis.

Table 1 Characteristics of patients and catheters in the NTG and control groups (*PRISM* Pediatric Risk of Mortality, *TPN* total parenteral nutrition, *IL* intralipid)

	NTG ($n = 21$)	Control ($n = 23$)	p value
Age (months)	9.5 ± 3.1	14.2 ± 4.1	0.4
Gender (M/F)	11/10	18/5	0.1
PRISM score	9.2 ± 1.4	11.7 ± 2.1	0.7
Catheter duration (days)	6.2 ± 1.0	8.6 ± 1.0	0.1
No. of insertion attempts	1.9 ± 0.3	3.3 ± 0.9	0.3
TPN or IL infusate	2 (10%)	6 (26%)	0.2
Total thrombi	7 (33%)	5 (22%)	0.6
Mural thrombi	4 (57%)	3 (60%)	1.0
Fibrin sheath thrombi	3 (43%)	2 (40%)	1.0

Statistical methods

The primary outcome variable was the difference in the incidence of ultrasound-diagnosed thrombosis between the NTG and control groups. Secondary outcome variables included: (1) difference in clinical evidence of thrombosis between the two groups; (2) difference in the incidence of catheter-related infection between the two groups; (3) impact of TPN, intralipid and heparin infusions on thrombosis in each group; and (4) impact of duration of catheter placement on thrombosis in each group. Sample size estimates were based on the primary outcome variable. Based on previous investigations [2, 3], we expected to find a 40% incidence of thrombosis in the control group and a 10% incidence of thrombosis in the NTG group. Given an alpha (2-tailed) = 0.05 and beta = 0.2, 31 patients were needed in each group for a total of 62 patients. An interim analysis was planned after two-thirds of the study patients had been enrolled. Demographic data were analyzed by descriptive statistics (mean, standard error of the mean). The differences between NTG and control groups, as well as thrombosis and no thrombosis groups, were analyzed by chi-square tests for categorical data and by the Student's t test for parametric, and the Mann Whitney U-test for non-parametric, continuous variables. Probability values of less than 0.05 were considered significant.

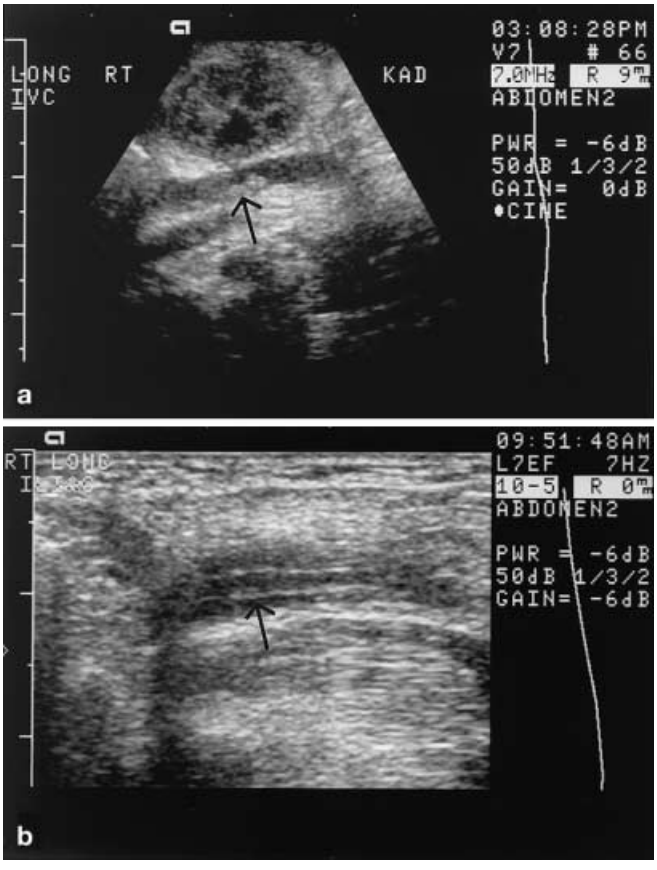

Fig. 1a, b Ultrasound images of mural and sheath catheter-related thrombosis. (**a**) Longitudinal image of the inferior vena cava just cranial to the iliac veins revealing a lumen occluded with an echogenic, irregularly contoured mural thrombus *(arrow)* (**b**) Longitudinal image of the right iliac vein demonstrating a sheath thrombus that mimics the shape of the catheter recently removed from the right groin *(arrow)*

Results

The trial was terminated after the interim analysis revealed no statistical significance in the primary outcome variable. Fifty-three patients were enrolled in the study and 44 patients (mean age 12.0 ± 2.6) completed the study (21 in NTG group, 23 in control group). The mean Pediatric Risk of Mortality (PRISM) score was 10.5 ± 1.3 representing a predicted risk of mortality of 4.3%. The actual mortality rate was 2.3%. Underlying diagnoses included: respiratory failure (18), sepsis (9), neurologic disease (7), airway reconstructive surgery (4), gastrointestinal disease (4), severe combined immunodeficiency (1) and postoperative cardiac surgery (1). Nine patients were excluded from the study analysis because: the patient was transferred to a floor where protocols did not permit infusing the study drug (3), the patient was discharged before the second ultrasound was performed (2), the study drug was not infused due to drug incompatibilities (2), the infusion port clotted prior to starting study drug (1) and patient death during the study without performance of an autopsy (1). Patient and catheter characteristics in the two study groups are noted in Table 1.

The mean duration of catheter placement for all study patients was 7.5 ± 0.7 days. Twelve of 44 patients (27%) had thrombi: 7/21 in the NTG group; and 5/23 in the control group (p = NS). Figure 1 demonstrates ultrasound images of a study patient with a mural thrombus and one with a sheath thrombus. Patient and catheter characteristics are compared between patients with and without catheter-related thrombi in Table 2. There were no differences between those children with and without thrombi in age, gender, PRISM score, number of insertion attempts, duration of catheter placement,

Table 2 Characteristics of patients and catheters in subjects with and without catheter-related thrombosis (*PRISM* Pediatric Risk of Mortality, *TPN* total parenteral nutrition, *IL* intralipid)

	Thrombus present ($n = 12$)	Thrombus absent ($n = 32$)	p value
Age (months)	7.7 ± 2.4	13.6 ± 3.4	0.3
Gender (M/F)	7/5	22/10	0.7
PRISM score	13.0 ± 3.6	9.5 ± 1.2	0.4
Catheter duration (days)	6.4 ± 1.2	7.8 ± 0.9	0.4
No. of insertion attempts	2.6 ± 0.5	2.7 ± 0.7	0.4
TPN or IL infusate	1 (8%)	7 (22%)	0.4
Clinical signs of thrombosis	4 (33%)	6 (19%)	0.4
Infection	1 (8%)	2 (6%)	1.0

clinical signs or symptoms of thrombosis, or number of infections. Positive blood cultures were noted in 1/23 (4.3%) patients in the control group, and 2/21 (9.5%) patients in the NTG group (p = NS). One patient with a positive blood culture was also diagnosed with a thrombus. No patients in the NTG group experienced hypotension or tachycardia secondary to the infusion (data not shown).

Discussion

Vascular thrombosis is common after placement of central venous catheters in children, with an incidence between 18 and 44% [2, 3, 22]. Catheter-related thrombosis can lead to significant complications in children including pulmonary embolism rates as high as 16% and mortality rates of 3.6% [29]. Catheter-related thrombosis is a multifactorial process involving the interaction of the vascular endothelium and the catheter surface. Factors derived from the vascular endothelium that insure an antithrombogenic state include NO, prostacyclin, heparan sulfates, adenosine diphosphatase, tissue type plasminogen activator and thrombomodulin [30]. NO and prostacyclin provide antithrombogenic properties through inhibition of platelet adhesion and aggregation. Insufficient NO production has been implicated in the pathogenesis of vascular thrombosis [31]. NO increases the level of platelet cyclic GMP via activation of guanylate cyclase [7, 8] resulting in diminished platelet adhesion and aggregation [9, 10, 32]. Glycoprotein Ib is important in the adhesion of platelets to damaged endothelium. Patients treated with inhaled NO have diminished platelet glycoprotein Ib surface expression [33]. NO inhibition of platelet aggregation is thought to be mediated by reduction in fibrinogen binding to the platelet glycoprotein IIb/IIIa receptor [34]. In addition to the effect of NO on platelet activity, it also increases the levels of vascular smooth muscle cell cyclic GMP [7, 8], resulting in smooth muscle relaxation and modulation of blood vessel wall tone. Finally, NO stimulates endothelial release of prostacyclin, a vasodilator [11], and inhibits endothelin-1, a potent vasoconstrictor [12].

Nitroglycerin has been used as an antianginal agent since the late 1800s because of its ability to relax venous and arterial smooth muscle. In addition to its effects on blood vessel tone, NTG has potent anti-platelet effects. It is believed to exert its overall activity via biotransformation to NO in plasma [35]. Animal and human studies suggest that NTG has potent antithrombotic and antiplatelet activity [13, 14, 15, 16, 32, 34, 35]. We hypothesized that, given its venodilating (flow enhancing) and antithrombotic properties, NTG might reduce the incidence of catheter-related venous thrombosis. Our data, however, did not support a protective effect of NTG infusion on catheter-related thrombosis.

There are several possible explanations for our findings. First, the dose of NTG utilized may have been inadequate. We selected a NTG dose of 0.1 mcg · kg · min as having a reasonable likelihood of success. Plasma NTG concentrations of 2 ng/ml or more have been shown to inhibit platelet aggregation in humans [17, 18], and adult NTG doses of 3.4–440 mcg/min (equivalent to 0.05–6.3 mcg · kg · min), produce plasma concentrations ranging from 0.4 to 481 ng/ml [19]. We did not measure NTG plasma concentrations or platelet function in the study patients and it is possible that study patients did not achieve sufficient levels to inhibit platelet function. A higher dose of NTG may have had greater antithrombotic effect, however, it is likely that concomitant hemodynamic effects would have occurred. Aoki et al. demonstrated inhibition of platelet function using a NTG infusion of 4–8 mcg · kg · min in adult patients undergoing orthopedic surgery [35]. This dose is 40–80 fold higher than the dose used in the current study.

Second, the local NTG concentration may have been insufficient to prevent thrombosis at the site of catheter-related endothelial injury, vessel obstruction and turbulent flow. We had postulated that an infusion delivered through the proximal lumen of a multi-lumen catheter would provide maximal exposure of the catheter surface and surrounding vessel wall to high local infusate concentrations. However, blood flow naturally carries infused NTG away from the site of catheter entry, which may have resulted in sub-optimal local anticoagulant effects. Third, NTG has an inhibitory effect on platelet NO synthase activity [36]. This NO synthase downregulation may contribute to the nitrate tolerance that is seen with prolonged continuous NTG infusion and may explain the lack of antithrombotic effects in the NTG group patients. Fourth, blood vessel obstruction and turbulence at the site of catheter entry into the vessel may be principal factors in the initiation and propagation of thrombosis such that platelet inhibition would have little impact on this process. This premise is supported by

the observation that simple removal of a catheter from an area of catheter-related thrombosis often results in resolution of the thrombus. Fifth, patients in the NTG group were younger than those in the control group. Though not statistically different, this age variation is associated with a smaller vessel diameter and, thus, would favor increased vascular obstruction and turbulent flow in the NTG group. Finally, although there was not a trend toward an antithrombotic effect in the NTG group, patient enrollment numbers in the study did not allow exclusion of a type 2 statistical error.

In this study there was a 27% incidence of catheter-related femoral venous thrombosis, consistent with previous prospective trials in children [2, 3, 22]. The majority of the thrombi were characterized as mural, while 45% were thrombi encasing the catheter only (fibrin sheath). Variables such as age, gender, duration of catheter placement, insertion attempts or type of infusate did not appear to influence the development of thrombosis. In our previous study we noted that 31% of patients with femoral venous thrombosis had no clinical evidence of the process [2]. In the current study, we noted that 67% of patients had no clinical evidence of thrombosis. These thrombi would not have been detected without prospective imaging studies. The difference in the incidence of clinical signs of thrombosis between the studies can probably be attributed to the significant number of fibrin sheath thrombi in the current study, in comparison to mural thrombi in the previous study. Fibrin sheath thrombi are less likely to obstruct the vessel lumen and result in clinical signs.

In conclusion, intracatheter NTG infusion did not reduce the incidence of catheter-related thrombosis in children in this randomized, controlled trial. Nonetheless, the use of NO donor compounds for this purpose warrants further study. Methods that result in higher local NO concentrations at the damaged endothelium site while minimizing systemic NO effects may yet prove to be useful in the prevention of venous thrombosis. Future studies should be conducted in patients receiving hemodynamic-range doses of NTG with concomitant measurement of NTG plasma levels to insure that antiplatelet concentrations are reached. Sampling of plasma NTG levels should occur at the distal catheter port along with a site peripheral to the infusion to confirm that local plasma concentrations are greater than systemic concentrations. We are currently studying catheters coated with soluble slow-release NO donors (NONOates) [37]. These compounds have the potential to have local antithrombotic activity and metabolism while avoiding systemic activity.

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