Thrombolysis is increasingly considered in the treatment of venous thrombosis in children to prevent organ infarction as often occurs following renal vein thrombosis, or to preserve venous blood flow. Currently, streptokinase is not advised for use in children owing to the high prevalence of neutralizing anti-streptococcal antibodies. Urokinase derived from human renal epithelial cells is no longer approved by the US FDA secondary due to safety concerns. To date, there have been no formal recombinant tissue plasminogen activator (tPA) dose-finding studies in infants and children. In addition, there are no level 1 randomized, prospective studies comparing tPA to other therapies in pediatric patients. This report will summarize all published case series with three or more pediatric patients in the English literature in which sufficient information was given in order to make recommendations for current practice (1-3).

Arterial Thrombosis

For arterial thrombosis, tPA was given in a median dose of 0.3 mg/kg/h without a loading dose for a median duration of approximately 12 h. Efficacy of tPA thrombolysis in children was excellent. Complete clot lysis results in 97% of infusions with partial lysis in 3%. Bleeding complications occurred in 54% of all treated children with major hemorrhage (gastrointestinal or requiring packed cell transfusion) in 11% and minor hemorrhage in 43%. One child required a limited amputation of an affected arm and one child died of the underlying disorder (3).

Venous Thrombosis

tPA thrombolysis has been reported in series totaling 34 non-neonatal pediatric patients with venous thrombosis. While initial dosing of tPA was similar to that reported for arterial clots, more recent experience with very low tPA dosing (0.03 to 0.1 mg/kg/h) has shown efficacy equal to use in higher doses. Complete clot lysis was reported in 70% with partial lysis in 9% and no lysis in the remaining 21%. Reported bleeding complications of tPA in children included gastrointestinal bleeding in 3%, oozing at the infusion site in 44% (including a hematoma in one), and restlessness and agitation in 3%. Two of thirty-four (6%) children died of multi-organ failure and one (3%) had slight limb swelling in follow-up.

Neonatal Arterial Thrombosis

Neonates in initial series were given higher doses of tPA (0.5 mg/kg/h:1). Recent series indicate usage of lower doses with no loss in efficacy, similar to experience in older children (3). Complete clot lysis was documented in 75%, partial lysis in 20% and no lysis in 5%. Major intracranial hemorrhage occurred in 10% of infants (high-risk preterm infants receiving the highest dosage of tPA (0.5 mg/kg/h) without suffering from thrombocytopenia or hypofibrinogenemia). Minor bleeding occurred in 50%, primarily at the site of infusion.

Neonatal Venous Thrombosis

tPA infusion was administered in 23 neonates with venous thrombosis (1, 2). TPA thrombolysis resulted in complete clot lysis in 56%, partial lysis in 35% and no lysis in 9% of newborn infants. Major hemorrhagic complications occurred in three infants (13%), two who developed intracranial hemorrhage in association with evidence of perinatal asphyxia or extreme prematurity and one with gastrointestinal bleeding. Both infants with intracranial hemorrhage were thrombocytopenic. No minor bleeding was reported in this group of infants. The outcomes of neonates were consistent with the severe nature of their underlying conditions.
Clearance of Obstructed Catheters

Indwelling central venous catheters have a high rate of occlusion. A subsequent randomized, double-blind clinical trial confirmed that tPA was superior to urokinase in clearance of radiographically proven central venous catheter thrombosis (4). In vitro studies have demonstrated the stability of stored tPA in concentrations of 0.5 to 2 mg/ml for 14 days at 20° C immediately after dilution or following two weeks of freezing (5). A recent pediatric study reported 89% efficacy of tPA overall, with no difference between 0.25 and 0.5 mg dosage.

Conclusions

tPA has shown efficacy in thrombolysis of arterial as well as venous thromboses in pediatric patients. Bleeding toxicity was comparable in all four groups reported with major hemorrhage in approximately 10%. Minor bleeding occurred in almost half of treated patients. Both arterial as well as venous lesions showed similar efficacy with low-dose (<0.1 mg/kg/h as compared with high-dose therapy (0.5 mg/kg/h).

Recommendations

1. The primary use of tPA thrombolysis of vascular thrombosis in children should be in the conduct of clinical trials.
2. Concomitant heparin, when used, should be administered in prophylactic doses.
3. Standard contraindications to thrombolysis should be observed in pediatric patients to decrease hemorrhagic complications (major surgery or hemorrhage within 10 days of therapy, a severe asphyxial event within 7 days of therapy, invasive procedure within 3 days of therapy, seizures within 48 h of therapy, prematurity <32 weeks gestation, systemic septicemia, active bleeding at the time of therapy, inability to maintain platelets >50,000/μl or fibrinogen >100 mg/dl).
4. Local instillation of tPA to clear obstructed central venous catheters is safe and efficacious in newborn infants and children. To decrease cost, the lowest effective dose (0.25 to 0.50 mg/ml) should be employed.

References


Received April 15, 2002 Accepted April 15, 2002