Thrombolysis Using Tissue Plasminogen Activator: Experience from a Critical Care Setting

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Abstract To describe the experience of thrombolysis using tissue plasminogen activator (tPA) in critically ill children admitted to the pediatric intensive care unit (PICU), retrospective review of medical records of all children (1 month–16 years), who were admitted in PICU since January 2014 to December 2017 and received systemic tPA for thrombolysis was done. Data was collected on a structured proforma and included thrombus location, tPA dose and duration, outcome (resolution, survival) and complications (bleeding). Total 9 patients (7 males, 2 females) received systemic tPA therapy for thrombolysis with mean age of 74.64 ± 69.58 months. Two patients had thrombus in femoral artery, 3 in IVC and 4 had intra-cardiac thrombosis. Median number of doses was 2 with a range of 1–5 doses. Complete resolution of the clot was noted in all except one patient. A standard starting dose of

0.01 mg/kg/h was used in all patients. Only one patient developed melena after TPA therapy which self-resolved. Systemic tPA therapy was very safe in pediatric critically ill patients and was effective for thrombolysis and did not show any adverse effects in children with varying underlying diagnosis.

Keywords Systemic tPA · Children · Thrombolysis

Introduction

Venous and arterial thromboembolic events (TE) are increasingly recognized in infants and children with a three–tenfold increase in the frequency of TE in hospitalized children over the last 15 years [1]. This is due to increasing survival of children with chronic complex problems, more use of central venous catheters (CVC) in critically ill children, and improved imaging modalities for accurate and timely diagnosis [1]. Critically ill children are at especially high risk for development of TE [2, 3]. The underlying etiology is usually multifactorial including presence of CVC, underlying cardiac disease/cardiac catheterization, various hematological/oncological conditions and genetic causes [4]. The acute risks of thrombosis include vascular obstruction which can be limb threatening, thrombus propagation and embolism, and nidus for infection and these can be life threatening needing immediate thrombolysis/thrombectomy [5]. Therefore, effective and timely treatment of these life-threatening cases with thrombolytic drugs is required, with tissue plasminogen activator (tPA) being one of the choices [6]. Despite the increase in use of tPA for thrombolytic therapy in children, the evidence regarding safety and efficacy continues to be dominated by case reports [5, 7, 8]. There is limited

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published information on the dose and duration which presents a challenge to the practitioner. We sought to review our experience with tPA in critically-ill children with different primary diagnoses with specific goal to determine the safety and effectiveness in terms of clot resolution with the use of tPA in a critical care setting.

Materials and Methods

A retrospective review of medical records of all children (aged 1 month–16 years) who received systemic tPA for thrombolysis in our 8 bedded pediatric intensive care unit was done after approval from the ethical review committee of the university (4893-PED-ERC-17). All the patients with a proven TE are started on Heparin infusion after loading dose. tPA therapy was decided based on the type and location of clot and potential for complications. tPA infusion was used as per existing guidelines, with a dose of 0.1U/kg/h for 6 h daily [9]. Concomitant heparin infusion was given in all cases, and coagulation parameters (prothrombin time, partial thromboplastin time, international normalization ratio), fibrinogen, platelets count and hemoglobin were monitored at least daily and when needed. A 10 ml/kg dose of fresh frozen plasma was transfused daily before tPA infusion to increase plasminogen levels, and platelets were transfused if counts were < 100. All patients who received tPA in our case series were intubated, sedated and paralyzed, positioning was restricted and suction was withheld during tPA infusion, while urinary catheter was inserted before starting the therapy, and arterial puncture and other invasive procedures were avoided. The presence of thrombosis was confirmed by color Doppler ultrasound (USD) examination and computed tomographic angiography (CTA) almost always before giving tPA. Follow-up USD/echocardiography were performed daily and then further therapy was decided. *Clot resolution* was divided into: (1) No resolution, (2) Partial resolution, (3) Complete resolution. For arterial thrombi, complete clot resolution was return of a peripheral pulse by palpation. Partial resolution was return of a peripheral pulse intermittently. This was confirmed by objective testing through USD, echocardiography and/ or CTA, as required. Complete resolution of other types of clots was ‘no clot detected by objective testing after tPA doses’ and partial resolution was ‘reduction of clot size’.

The data was collected on a structured proforma. Details of tPA prescription were retrieved from pharmacy records, patient charts and nursing documentation. Data collection included demographic information (age, gender etc.), clinical information, laboratory data (hemoglobin levels, platelets, prothrombin time, international normalization time, prothrombotic work and radiological studies done)

and outcome data (length of hospital stay, clot resolution, survival and cause of death in case of death). Data was entered and analyzed using SPSS version 20. The results are presented as mean with standard deviation and frequency with percentage.

Results

Nine children, (seven males and two females) with mean age of 74.64 ± 69.58 months (minimum 2 months, maximum 17 years) underwent thrombolysis with tPA during the study period. Primary diagnosis included fulminant myocarditis in 2 patients, and one each with tetralogy of fallots repair, transposition of great arteries post atrial septostomy, acute respiratory distress syndrome with multiorgan dysfunction and IVC thrombus, thalassemia major with cardiomyopathy, dilated cardiomyopathy, infective endocarditis with large vegetation on mitral valve obstructing the outflow and hip osteomyelitis with deep venous thrombosis. Location of thrombus included femoral artery in 2 patients, intracardiac thrombus in 4 and in IVC in 3 patients. Amongst the intracardiac thrombi, two children with congenital heart disease had left ventricular thrombus, while one had a right sided thrombus. Patient characteristics are detailed in Table 1.

Number of doses required ranged from 1 to 5 with a median of 2 doses. Mean time from TE to tPA therapy in patients who developed thrombosis during hospital stay was 5.5 h. Complete resolution of the clot was noted in all the patients except one (hip osteomyelitis). One patient developed melena, secondary to tPA infusion with 4 g/dl drop in haemoglobin but hemodynamics remained stable. No complications were observed in rest of the patients. The degree of clot resolution was not significantly related to age of the patients or tPA duration.

Discussion

Critically ill children are increased risk of life threatening TE so thrombolytic therapy is needed in many cases to resolve the clots. In recent years, tPA has been increasingly favoured over other thrombolytic agents [2, 4]. Physiologically, tPA offers specific and strong binding to fibrin, leading to preferential activation of only plasminogen bound to fibrin [6]. Furthermore, the short plasma half-life of tPA (about 5 min) compared with streptokinase, and the potential for anaphylactic reactions associated with the repeated use of streptokinase make the use of tPA more desirable. Our case series provides an assessment of thrombolysis using tPA in the PICU.

Table 1 Patients characteristics who received tissue plasminogen activator

Patient number	Age (months)/gender	Primary diagnosis	Location of thrombus	tPA indication	No of days of tPA therapy	Clot resolution	Patient outcome
1	40/male	d-transposition of great arteries, post atrial septostomy	Femoral artery thrombus	Limb threatening	5	Complete	Survived
2	50/male	Fulminant myocarditis	Left ventricle and internal carotid artery	Large thrombus with risk for stroke	4	Complete	Expired
3	204/male	Thalassemia major with cardiomyopathy	Left ventricle	Large thrombus with risk for stroke	1	Complete	Expired
4	50/male	Tetralogy of fallot repair	Femoral artery	Limb threatening	3	Complete	Survived
5	144/male	Diphtheria myocarditis	Inferior vena cava	Total obstruction of IVC	2	Complete	Expired
6	120/male	Hip osteomyelitis	Inferior vena cava	Total obstruction of IVC	5	Not resolved	Survived
7	108/male	Infective endocarditis	Left ventricle	Large thrombus with risk for stroke	2	Complete	Survived
8	54/female	Acute respiratory distress syndrome with multiorgan dysfunction	Inferior vena cava	Total obstruction of IVC	2	Complete	Expired
9	28/female	Dilated cardiomyopathy	Left ventricle	Large thrombus with risk for stroke	1	Complete	Survived

Gupta et al in their largest case series of 80 children showed successful clot resolution using tPA in 65% of their patients with 40% developing major complications [5]. They used a dose of 0.1–0.5 mg/kg/h. In contrast, Wang et al reported that a significantly lower dose of tPA, 0.01–0.06 mg/kg/h for less than 24 h, was equally effective at thrombolysis, but with lower rates of bleeding complications [10]. Hence, there is a reported range of dosage of tPA for children between 0.01 up to 0.6 mg/kg/h. Hartmann et al have also shown complete resolution in 78% of neonates treated with a continuous infusion of 0.2 mg/kg per h of tPA [11]. We used dose of 0.1 mg/kg/h for 6 h daily in all our patients. Complete resolution of clot was observed in all our patients except one who had deep venous thrombosis involving whole inferior vena cava secondary to hip osteomyelitis making tPA very successful for clot resolution. And except one patient who had minor bleeding episode there was no other adverse effect of tPA observed. Number of days of tPA therapy did not correlate with the complete clot resolution.

Our results have the limitations of being a retrospective study, with a small sample size. We also do not have a control group to compare the long term patient outcomes. However, this case series is the first from the country and with complete clot resolution in eight out of our nine patients, we can safely predict that tPA can be used for

thrombolysis in children. However, further larger trials are needed to define the efficacy of the use of tPA in critically ill children presenting with thrombi.

Conclusions

Systemic tPA therapy was very safe in pediatric critically ill patients was effective for thrombolysis and did not show any adverse effects in children with varying underlying diagnosis. Number of days of tPA therapy did not correlate with the complete clot resolution.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval Aga Khan University 4893-PED-ERC-17.

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