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ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Tissue plasminogen activator for neonatal coronary thrombosis presenting with mitral valve regurgitation and impaired ventricular function

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Abstract

Objective: Neonatal coronary thrombosis is a rarely reported disorder, with variable outcomes described. This study assessed the feasibility and safety of an institutional protocol using tissue plasminogen activator (tPA) administration for the treatment of neonatal coronary artery thrombi.

Methods: They reviewed the outcome of three neonates with clinical evidence of myocardial infarction secondary to coronary thrombosis. All three underwent the tPA treatment protocol.

Results: The three described cases presented at 5 hours, 15 hours, and 10 days of life. The patients identified underwent the tPA protocol at least once. There was clinical evidence of improvement in coronary flow, as well as demonstration of increased left ventricular function and decreased mitral regurgitation. No major adverse events occurred.

Conclusion: Thrombolytic therapy with this tPA protocol may be safe and effective in treating neonates with coronary thrombosis.

KEYWORDS

coronary thrombus, neonatal mitral regurgitation, neonatal impaired ventricular function, tPA

1 | INTRODUCTION

Neonatal coronary thrombosis has been described in several case reports and series, but there remain few data describing the overall prevalence of the disease and there is no consensus on optimal treatment.[1–3] It can result in significant morbidity due to myocardial ischemia or infarction, associated decrease in ventricular function, and papillary muscle infarction causing mitral regurgitation.[4,5] Thus, timely and effective treatment strategies are needed. Thrombolytic treatment using tPA for neonates with non-coronary thrombus formation has been shown to be safe and effective for thrombolysis in multiple studies.[6,7] Individual cases of coronary artery thrombosis have been treated with thrombolytic therapy with mixed results.[8–12] The purpose of our study is to report the use of a tPA protocol for treatment of neonates presenting with coronary thrombosis along with a review of the literature.

2 | METHODS

Patients with evidence of myocardial infarction and suspected coronary thrombosis on the basis of clinical presentation were taken to the catheterization laboratory to perform a coronary artery angiogram to evaluate for coronary artery thrombosis. In each case, one or more coronary thrombus was identified and the treatment protocol was initiated (Figure 1). Prior to tPA administration, patients were evaluated to ensure none had any active bleeding. Patients were considered suitable for tPA protocol if their fibrinogen level was more than 150 mg/dL.

3 | RESULTS

The three cases of neonatal myocardial infarction involving coronary artery thrombosis are described. Patients presented at 5 hours, 15 hours, and 10 days of life. Only one patient had a normal

electrocardiogram and a normal troponin levels. Two of the patients had elevated troponin levels and abnormal electrocardiograms (ECG) consistent with myocardial ischemia. The third patient was suspected to have coronary thrombosis on the basis of decreased left ventricular function and mitral regurgitation without another explanation. All three patients received tPA treatment per our institutional protocol and demonstrated rapid improvement in the degree of mitral regurgitation (MR) and in left ventricular systolic function. No major adverse events such as cerebral hemorrhage, pulmonary hemorrhage or gastrointestinal hemorrhage were identified. In all cases, the hypercoagulability work ups were negative, and the cause(s) of thrombosis were not identified. The clinical improvements were sustained for each patient through a follow up period ranging up to 6 months.

3.1 | Case #1

A 3.06 kg female infant was born at 40 weeks gestation and delivered by normal spontaneous vaginal delivery. The pregnancy was complicated by maternal lupus. A prenatal fetal echocardiogram was normal. Evaluation of the placenta revealed no evidence of thrombus. She was clinically stable until 5 hours of life when she was noted to have respiratory distress and hypoxemia. An echocardiogram demonstrated mild mitral regurgitation and hypokinesis of the posterior and lateral portions of the left ventricle. An electrocardiogram (ECG) demonstrated T wave inversion in the lateral leads. Troponin t level was 0.11 ng/mL (normal $<$ 0.05 ng/mL). Cardiac catheterization performed at 15 hours of life showed small thrombi in the proximal right coronary artery (RCA), diminished flow in the left anterior descending artery (LAD), and absence of distal flow in the left circumflex coronary artery (LCx). The treatment protocol (Figure 1) was administered. She was extubated on post procedure day #2 and transitioned to subcutaneous low molecular weight heparin (LMWH) and aspirin for 3 months duration. A follow-up echocardiogram demonstrated resolution of MR and normalization of the left ventricular systolic function, and no evidence of regional wall motion abnormalities. At the latest follow up (5 months of age), she continues to have no MR, normal left ventricular systolic function and no regional wall motion abnormality.

3.2 | Case #2

A 4.01 kg male infant was born at 40 weeks gestation and delivered by normal spontaneous vaginal delivery after an uncomplicated pregnancy. The placenta and umbilical cord were normal and without evidence of thrombus based on pathologic evaluation. At 15 hours of life, he was found to be tachypneic and hypoxemic. He was brought to the NICU (from newborn nursery) and was found to have severe acidosis (pH 6.95, base deficit 17). He was intubated and started on empiric antibiotics. His chest x-ray was notable for small pleural effusions bilaterally and pulmonary edema. The ECG was unremarkable and troponin on admission was 0.03 ng/mL (normal-$<$0.05 ng/mL). The initial echocardiogram revealed severe mitral regurgitation, moderate tricuspid valve regurgitation, a large patent ductus arteriosus with right to left shunting, severe right pulmonary

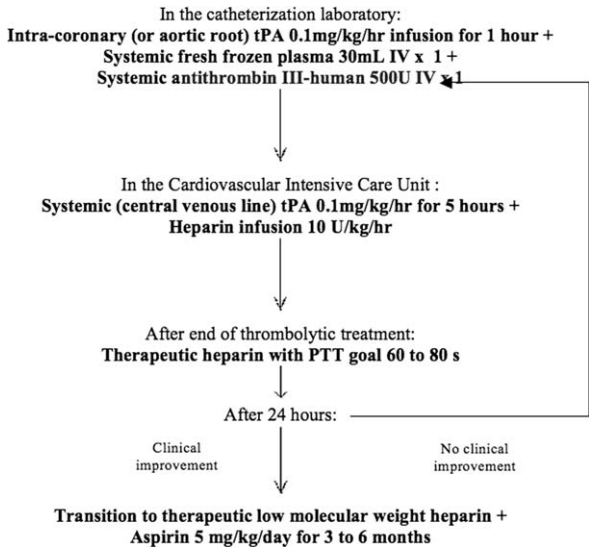

FIGURE 1 Algorithm for thrombolytic therapy with tPA. Local tPA is administrated in the cardiac cath lab via a 4 Fr Glide catheter directed toward the origin of the coronary artery, or with direct infusion into the coronary artery. Systemic fresh frozen plasma is given to optimize effective thrombolysis Systemic tPA is administrated via central line if fibrinogen level is more than 150 mg/dL. Systemic antithrombin III is given to optimize heparin properties

hypertension, and mildly diminished left ventricular systolic function. He required mechanical ventilation and inotropic support. No etiology for the mitral valve regurgitation was identified. On day of life (DOL) #14 a cardiac catheterization was performed and angiography demonstrated a mobile thrombus in the left main coronary artery (LMCAdiminished flow in the LAD, no flow in the distal LCx (Figure 2), and a small thrombus in the proximal RCA (Figure 3). Left ventricular end-diastolic pressure (LVEDP) was 25 mm Hg. Thrombolytic treatment with tPA was started.

On DOL #15, a second cardiac catheterization demonstrated improved flow to the left coronary artery system and resolved right coronary artery thrombus. His LVEDP had decreased to 16 mm Hg. He received another dose of local and systemic tPA infusion (see Figure 1). Eight hours later, repeat cardiac catheterization showed no coronary artery thrombus and LVEDP of 9 mm Hg. He remained intubated requiring mechanical incubation and inotropic support postprocedure. He was successfully extubated on DOL #25. He was transitioned to subcutaneous lovenox, aspirin, and oral medical management of left ventricular dysfunction. On DOL #34, his predischarge echocardiogram showed mild MR and normal left ventricular systolic function with no regional wall motion abnormality. At latest follow up (at 4 months of age), he had trivial MR and good biventricular systolic function.

3.3 | Case # 3

A 2.787 kg female infant was born at 38 weeks gestation and delivered by normal spontaneous vaginal delivery. The pregnancy was uncomplicated. She did well after delivery and was discharged home. She

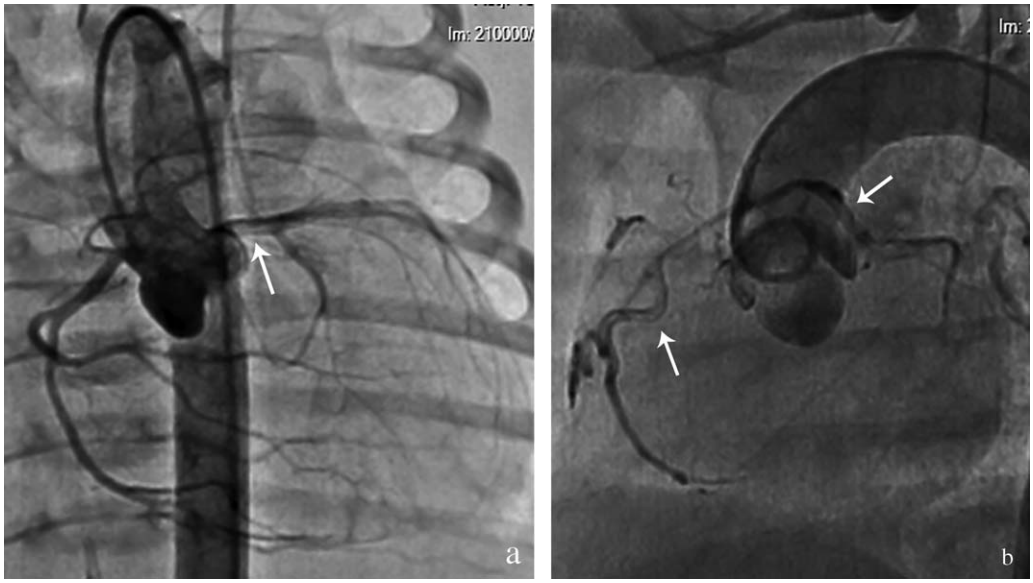

FIGURE 2 Aortic root injection in AP (a) and lateral (b) views demonstrating lack of filling of left coronary system and suggested thrombus (arrows).

presented at 10 days of age with severe cardiogenic shock, profound acidosis and required intubation and inotropic support. The initial echocardiogram (DOL #11) revealed moderate MR, regional wall motion abnormality (left ventricular posterior wall), a left ventricular EF of 39%, and an echobright appearance of the base of the interventricular septum. The initial electrocardiogram showed decreased voltages in the lateral leads. The troponin on admission was 12.79 ng/mL (normal- $<$0.04 ng/mL). On DOL #11, she reportedly had an episode of seizure-like activity and was started on phenobarbital. A brain MRI showed a small occipital subdural hemorrhage. On DOL #27, she was transferred to our hospital for heart transplant evaluation.

On DOL #36 a cardiac catheterization showed partial occlusion of the proximal LAD and near complete occlusion of the proximal LCx (Figure 4). The right coronary artery was patent. Systemic heparinization and thrombolytic treatment with tPA was started based on our protocol (Figure 1). Post procedure, she received nitroglycerin infusion for 11 hours to prevent any coronary artery vasospasm. Given her previous history of small occipital subdural hemorrhage, she was closely monitored after tPA infusion and no evidence of intracardiac hemorrhage or other adverse events from tPA infusion were noted. She was extubated after the procedure and was transitioned to subcutaneous LMWH and aspirin, and oral medical management of left ventricular dysfunction. The predischarge echocardiogram (DOL #49) demonstrated mild MR and improved ventricular function to an EF of 46%. At the latest follow up (11 weeks), she had mild MR, an echogenic basal septum with hypokinetic motion and improved left systolic function (EF 54%).

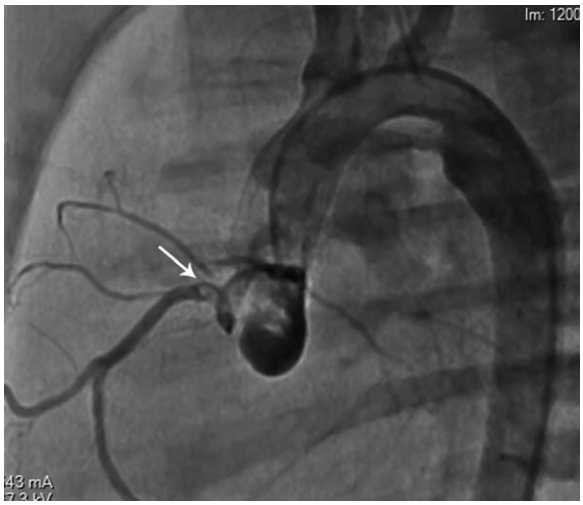

FIGURE 3 Filling defect in the origin of the RCA.

4 | DISCUSSION

Neonatal myocardial infarction is a rare entity in neonates without congenital heart and coronary malformations. Most cases of neonatal myocardial infarction are associated with thromboembolism and carry high mortality.[4] In 1947, Ravich and Rosenblatt were the first to describe two neonates who died suddenly after birth that had evidence of myocardial infarction on autopsy.[1] The typical presentation of myocardial infarction in the neonate is cardiogenic shock and respiratory distress. Most patients described in the literature had ECG findings consisting of ischemia, elevated cardiac enzymes, impaired ventricular function, and MR/TR.[13,14] MR discovered in a neonate can be due to either congenital or acquired causes.

Based on both the limited available published cases and our own experience, we believe that clinicians should have a high index of suspicion for coronary thrombosis as the primary cause of MR and impaired ventricular function in neonates without obvious causes such as

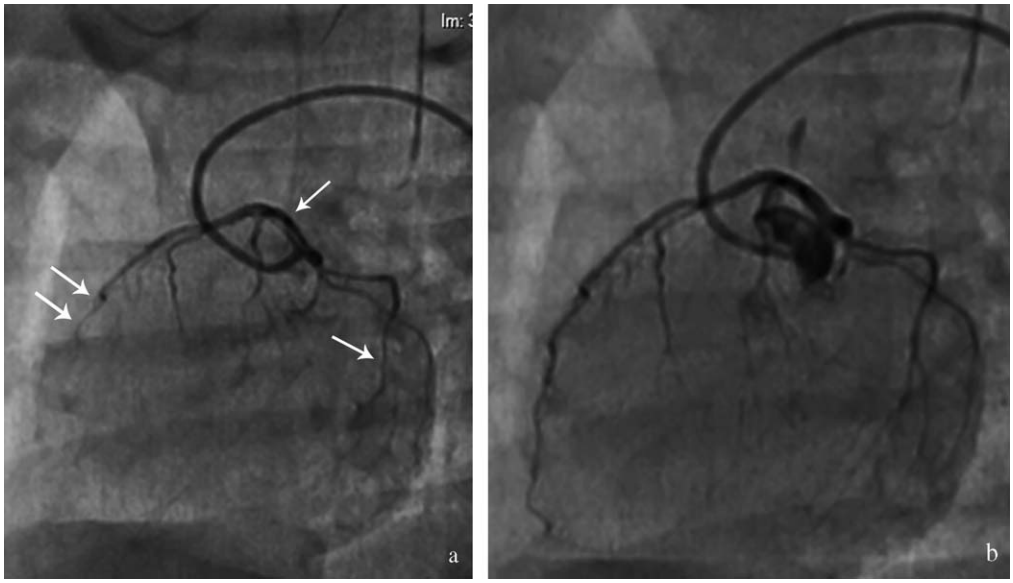

FIGURE 4 (a) Selective LMCA lateral angiogram showing multiple areas of subtle thrombi (arrows). (b) resolution of thrombi and better filling of distal branches.

coarctation or ALCAPA. Cardiac catheterization to evaluate the coronary vasculature should be considered as soon as possible if there is concern for ischemic induced cardiac pathology or unexplained moderate or severe MR.

The survival of neonates with coronary artery thrombosis is variable, and available treatments have shown mixed results (Table 1). A surgical thrombectomy was performed for the first time in a case of left main coronary artery (LMCA) thrombosis which resulted in the death of the neonate.[15] Thrombolysis therapy was performed in two case reports of neonatal myocardial infarction involving thrombosis of the LMCA, however both attempts were unsuccessful and the patients died.[8,9] ECMO support without thrombolysis therapy was successfully used in a neonate with myocardial infarction due to occlusion of the ramus intermedius branch of the left main coronary artery.[3] One case report described a neonate with myocardial infarction involving occlusion of the proximal left descending coronary artery (LAD) that was successfully managed by ECMO support and selective intracoronary tPA therapy.[10] Most recently, one case report described a neonate who developed an acute myocardial infarction from a thrombus at the bifurcation of the left anterior descending artery and left circumflex artery that was successfully treated with selective intracoronary tPA lysis and without ECMO support.[12]

Our small case series highlights the utility and safety of tPA for treatment of neonatal coronary thrombi by specific use of the described protocol. Multiple studies and cases series have reported successful use of tPA and streptokinase in treatment of neonates with non -coronary artery thrombi.[6,7,16,17] However, we could identify only three previous case reports of successful intracardiac tPA treatment of coronary artery thrombi.[10–12] The protocol described in our case series is our current standard approach. We believe that the protocol provides a safe and effective method for managing infants with mitral regurgitation and ventricular dysfunction resulting from coronary artery thrombi.

5 | CONCLUSION

Coronary arterial thrombosis should be suspected when evaluating a neonate with mitral valve regurgitation and ventricular dysfunction in the absence of other identifiable causes. Our report highlights the importance of prompt evaluation of coronary artery abnormalities with cardiac catheterization and the successful use of this tPA protocol in

TABLE 1 Previous reports of neonatal myocardial infarction

Author (years)	Thrombosis location	Treatment	Outcome
Ramlogan et al. (2014)[15]	LMCA	Surgical thrombectomy	Died
Abdurrahman et al. (1999)[8]	LMCA	TPA	Died
Tillett et al. (2001)[9]	LMCA	TPA	Died
Farooqi et al. (2012)[3]	Ramus intermedius branch	ECMO support	Alive
Deutsch et al. (2014)[10]	LAD	ECMO + TPA	Alive
Cesna et al. (2013)[11]	LAD	TPA	Alive
Hallbergson et al. (2015)[12]	Bifurcation of LAD and LCx	TPA	Alive

treatment of neonates with acute or subacute presentation of myocardial infarction from coronary artery thrombosis.

AUTHOR CONTRIBUTIONS

Delaram Molkara formed the concept of the manuscript, gathered the clinical information, reviewed all the imaging studies, drafted and edited the manuscript.

Jose A. Silva Sepulveda assisted in drafting the manuscript, the figures.

Thomas Do assisted in manuscript preparation and editing.

Christopher Davis assisted in literature search and editing.

Gregory P. Goldstein drafted one of the cases reported in the manuscript and contributed to the discussion section.

John W. Moore assisted in critical editing/revision of the manuscript.

Howaida G El-Said assisted in critical editing/revision of the manuscript, proposed tPA protocol, performed the cardiac catheterization procedure.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

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