# Assessment of Intravenous Thrombolytic Therapy in Children with Kawasaki Disease Complicated by Coronary Artery Thrombosis

Owen Healy
Mentor: Kevin G. Friedman
Affiliaton: Boston Children's Hospital

## Introduction

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is a disease in which blood vessels throughout the body become inflamed. 1 out of every 10,000 children younger than 5 are at risk of Kawasaki disease. Currently Kawasaki disease is the leading cause of acquired heart disease in children. Although there are treatment protocols in place for the management of myocardial infarction in young adults, there is no defined protocol for children. Data on efficacy and safety of thrombolytic agents for the treatment of KD patients with coronary artery aneurysm thrombosis and ongoing or impending myocardial infarction are missing.

## Methods

Patient data was collected between 1990 and 2019 from Boston Children's Hospital. Descriptive statistics were used to describe clinical, echo, and lab features of the group (n=10). The primary analysis was stratified by thrombolytic treatment within 10 days vs. thrombolytic agents at > 10 days of fever.

## Results

Results show that thrombolytic therapy leads to earlier resolution of coronary artery thrombus in KD compared to conservative anticoagulation management. Additionally, thrombolytic therapy is associated with an acceptable safety profile in relieving coronary artery blood-flow.

## Discussion

These findings confirm prior research. When the response rate was analyzed by treatment method, the response rate to thrombolytics was high even when considerable time (≥1 week) had elapsed since thrombus formation. Because of the small sample size, no definite conclusions about the efficacy of thrombolytics can be drawn, either alone or combined with another therapy. Despite these results, it is difficult to conclude that thrombolytics are not effective in cases in which several days or even a week or more has elapsed since thrombus formation. It is important to not rule out the possibility that even slight thrombolysis achieved by thrombolytics on the thrombus surface later enhances responses to thrombolytic therapy.

*1.0 Introduction*

Kawasaki syndrome, formally known as Kawasaki disease (KD), was first reported in 1967 by a Japanese pediatrician as an acute febrile syndrome. This pediatrician also discovered that it mainly affects the skin, mucosa, and lymph nodes[1]. Although initially recognized as benign, this syndrome was subsequently acknowledged to have a serious complication of coronary artery aneurysm.[2] KD is the leading and the most common form of childhood primary vasculitis and is the most common acquired heart disease in developed countries.[3,1-2] KD preferentially affects medium-sized, muscular, parenchymal arteries, particularly the coronary arteries.

Basic treatment of this disease consists of high doses of aspirin, and in some cases in vitro immunoglobulin (IVIG). With IVIG therapy, persistent CAAs are considerably less common but still occur in 4% to 6% of patients, with 1% developing giant CAA according to the Japanese Health Administration[23]. The incidence of coronary abnormalities is greater using z-score criteria.[4] A recent, 2center US study found that 2.6% of patients met the z-score definition for giant aneurysms. Patients with large or giant CAAs are at risk for cardiac events including CA stenosis, myocardial infarction, ventricular tachycardia, and death. Large case series of patients with giant CAA have shown good overall survival but high cardiac event rates.[5]

The vasculitis of Kawasaki disease causes coronary artery aneurysms in a few patients after or during the acute phase. Within a short amount of time, with correct treatment, the aneurysms usually change shape, or regress, but some may persist for years. In some cases, the aneurysms evolve into stenotic lesions, which are also known as stenotic strictures[7]. Stenotic lesions, also known as strictures, occur when narrowing of the coronary artery happens due to the contractions of smooth muscles[8]. In the late stages of Kawasaki disease, either new aneurysms or expanding aneurysms are unusual but have been reported in a few cases[9]. Although a full picture of the outcome of Kawasaki disease remains unclear, there is no doubt that coronary lesions are the predominant determinants of its outcome.[10] There are also other cardiovascular sequelae that could potentially affect the outcome. The only way these aneurysms can be found is through cardiovascular echocardiography, which is using sounds and photos to detect the parts of the heart heavily affected by the syndrome[11].

The process of echocardiography plays a vital role in the diagnosis and checking the treatment in KD. The doctors use a probe, called a transducer, which is then passed over your chest.[12] The probe produces sound waves that bounce off your heart and “echo” back to the probe. These echoes also use zscores to help with data imaging.[13] A z-score is the number of standard deviations from the mean a data

point is[16]. But more technically it's a measure of how many standard deviations below or above the population mean a raw score is. A z-score is also known as a standard score and it can be placed on a normal distribution curve[17]. These data points can help the doctors see which kinds of treatments which are helpful in the treatment of KD. When the results come in, the doctors can easily see if the patient has developed CAA. If there are, they will prescribe the patient with high doses of aspirin, and in some clinical trials, as previously stated, IVIG therapy has been proved to help with the regression of CAA[18].

As previously stated above, basic KD treatment consists of high doses of aspirin, and many different antibiotics, this is if the patient does not develop CAA[7]. These aneurysms can cause many different implications within the patient and the treatments they need. IVIG therapy has been crucial in the treatment of intensified CAA.[19] IVIG is the process of taking and purifying the plasma of donors and contains more than 95% unmodified immunoglobulin G.[20] Since the first demonstration of the effectiveness of IVIG in the treatment of immune thrombocytopenia purpura in 1981 it has been widely used to treat KD[23]. The immunomodulatory effects of IVIG are mediated through two different portions of the immunoglobulin. The F(ab´)2-dependent mechanisms include the killing of target cells by antibody-dependent cytotoxicity, the blockade of cell-cell interactions mediated by cell-surface receptors such as Fas and Fas ligand the neutralization of cytokines and autoantibodies, and the scavenging of the anaphylatoxins[24]. The IVIG, has played a vital role in the regression and treatment of CAA, and has also resulted in the search for new treatments. Many different doctors have tried to use the blood itself, instead of the specific immune globulin, which has had little success[25]. In one trial, consisting of 291 patients, IVIG therapy proved to be far more successful than any other type of treatment, however, it was not perfect.

In 2010 one of the first case series was written about intravenous thrombolytic agents. Antiplatelet and anticoagulants as well as streptokinase and urokinase were all described as effective intravenous thrombolytic agents[26]. Thrombolytic therapy for coronary aneurysm thrombosis of KD are intravenous coronary thrombolysis (IVCT) and Intracoronary thrombolysis or known as ICT[27]. Takashi et al in 2014 found that the best method of injection for These agents is through a peripheral intravenous line. In that study it was also found that administration must be used in sync with a low-dose aspirin and low-dose intravenous heparin[28].

Thrombolytic therapy has helped treat many different illnesses such as Crohn's disease and angina or ischemic chest pain. Before any other treatments or procedures doctors must use TPA, or tissue plasminogen activator, which is an enzyme that dissolves clots[28,29]. After completion of TPA heparin

dosage is increased. In 2011 it was found that coronary artery thrombosis should be reassessed with echocardiographic imaging after completion of the TPA infusion[13,17]. With successful intracoronary thrombolytic therapy a patient can remain healthy, that is of course with monitoring of coagulation parameters to prevent bleeding in maintaining the fibrinogen level and platelet count. A case series in 2018 focused on four patients, who were administered thrombolytic therapy to treat coronary artery thrombus.[22,26-28] All patients were above the age of three years old and it was concluded that IVCT and ICT were successful in decreasing the size of the CAA and myocardial infarction[30,28-29].

Despite appropriate IVIG therapy, one in four children with KD still develop coronary artery aneurysms, based on American Heart Association criteria, and ~1 % develop large/giant coronary artery aneurysms[7,10–12], which can put the child at risk for adverse cardiac events including, which include myocardial infarction (MI) and sudden death 4[,7,9,13]. Although there are treatment protocols in place for the management of MI in young adults, treatment of MI in children, particularly in the setting of KD, is an infrequent problem and thus data to develop evidence-based protocols and algorithms are lacking. Intravenous thrombolytic therapy has been proposed as a viable option for management of acute/subacute thrombosis in KD with CAA and ongoing or impending myocardial ischemia[14,15]. While, there no clinical trials or evidence-based recommendations on the use of thrombolytic therapy for the treatment of MI in pediatric patients, there are multiple case reports of the use of thrombolytic agents (both intracoronary and intravenous), in KD patients with CAA and thrombosis[14–19]. The largest series published to date is from data from the Japanese national survey which included 23 patients receiving thrombolytics (intracoronary n= 6, intravenous n= 12, both n=5) from 14 centers and reported that intravenous thrombolytics were more effective when thrombosis was smaller in size (< 10 mm) and when given earlier [20,21]. A recent publication outlining an approach to ST elevation MI (STEMI) in children with KD suggests using intravenous thrombolytics in STEMI if percutaneous coronary intervention is not feasible due to patient size or available personnel with PCI experience in this patient population[22]. Data on efficacy and safety of thrombolytic agents for the treatment of KD patients with CAA thrombosis and ongoing or impending MI are missing.

*2.0 Research Question and Hypothesis* Research
Question:

Primarily, is the use of thrombolytic therapy in KD patients with CA thrombus and impending or ongoing acute myocardial infarction effective - on individual patient level analysis - in reducing intracoronary thrombus burden +/- restoring coronary flow? Secondly, is the use of thrombolytic therapy associated with an acceptable safety profile?

$H_0$: Intravenous thrombolytic therapy will not be effective in relieving the CA thrombus.

$H_1$: Thrombolytic therapy leads to earlier resolution of coronary artery thrombus in KD compared to conservative anticoagulation (i.e., heparinization) management.

$H_2$: Thrombolytic therapy is associated with an acceptable safety profile in relieving coronary artery blood-flow.

## *3.0 Methods*

### *3.1 Study Design:*

Observational retrospective case series of cardiac outcomes in KD patients who received intravenous thrombolytics at Boston Children's Hospital.

### *3.2 Data Collection*

Data was collected between 2000 and 2019 from one institutional database, Boston Children's Hospital. The data consisted of both clinical and imaging data. The clinical data consisted of demographics (age, sex, ethnicity), KD history (typical vs. atypical, criteria for KD met), lab data, and treatment data (timing of treatment in KD course, which treatments: ICTV and ICT (how many doses), additional therapies (steroids, infliximab, cyclosporine, cyclophosphamide, abciximad, etc.). Imaging data was also collected if the patient data met the criteria. [See below] Imaging data consists of an initial echocardiogram, as well as a follow-up echo post treatment. The initial echo had z-score and absolute dimension for all coronary segments, degree of MR, left ventricular function, and effusion. The follow-up echo had maximum z-score and absolute dimensions over longitudinal follow- up, z-score and absolute dimensions at most recent follow-up, evidence of coronary artery thrombosis, size of coronary artery thrombosis, and coronary artery occlusion related to thrombosis.

### *3.3 Inclusion Criteria*

In order to be included in this study, there were three requirements. First, KD diagnosis at a participating institution between 2000 and 2019, treatment with an intravenous or intracoronary thrombolytic agent, and an available echocardiogram for a maximum of 10 days after treatment.

### *3.4 Exclusion Criteria*

There were multiple exclusion criteria for this study: patients seen at participating institutions for initial treatment with no available follow-up data, patients not treated with thrombolytic agents, patients with Congenital heart disease apart from bicuspid aortic valve, and patients with a hemodynamically

insignificant ventricular septal defect. Also, patients who received TPA at outside hospitals were not included in this study.

*3.5 Data Analysis*

Descriptive statistics were used to describe clinical, echo, and lab features of the group. Univariable and multivariable binary logistic regression analysis were used to evaluate for clinical, lab, and echo features associated with early CAA progression and for severe early CAA progression. The primary analysis evaluated only parameters available at the time of diagnosis (demographic/clinical/echo/lab) and did not include treatment or thrombolytic resistance parameters. The primary analysis was stratified by thrombolytic treatment within 10 days vs. thrombolytic agents at > 10 days of fever.

*3.6 Outcome Measures:*

In this study, the global rank endpoint will have several components, including measures of adverse cardiac events, coronary artery size as measured by z score, resistance to treatment, adverse events related to treatment, biomarkers of inflammation, duration of fever, length of hospital stay and parent observation of clinical improvement. A more detailed example of possible components and their ranks of the global rank endpoint for our study is as follows: Table 1. Outcome Measures

| Outcome Measure Rank | Rank |
|---|---|
| Death during study period | 1 |
| Heart transplant during study period | 2 |
| Major adverse cardiac event (myocardial infarction, CA thrombus, occlusion) | 3 |
| Giant CAA (maximal z-score >10.0 or absolute dimension > 8 mm) | 4 |
| Moderate CAA (maximal z-score >5.0, ≤10.0) | 5 |
| Primary treatment resistance (fever >24 hours after therapy completion) | 6 |
| Severe adverse event related to treatment | 7 |
| Moderate adverse event related to treatment | 8 |
| Mild CAA (maximal z-score >2.5, ≤ 5.0) | 9 |
| Abnormal biomarker data suggesting inflammation: i.e. CRP | 10 |
| Duration of fever ≥7 days | 11 |
| Length of stay in the hospital ≥ 14 days | 12 |
| Length of stay in the hospital 7 to 13 days | 13 |
| Parent observation: clinical worsening | 14 |
| Parent observation: no change in status | 15 |
| Parent observation: small clinical improvement | 16 |
| Parent observation: substantial clinical improvement at time of hospital discharge | 17 |

*4.0 Results 4.1 Tables*

Table 2. Demographics

| Patient Name | DOB | Sex | Ethnicity | Date of KD diagnosis | Age at KD diagnosis |
|---|---|---|---|---|---|
| Patient 1 | 01/05/06 | Male | White | 3/25/2006 | 3.5 months |
| Patient 2 | 8/22/06 | Male | White | 11/21/06 | 3 months |
| Patient 3 | 9/28/07 | Female | White | 08/29/2012 | 4 years, 11 months |
| Patient 4 | 04/12/02 | Male | White | 10/28/2012 | 10 years old |
| Patient 5 | 02/28/08 | Male | African-American | 07/05/2013 | 6 years old |
| Patient 6 | 01/30/12 | Female | White | 05/09/2017 | 5 years old |

Table 3. Medication administered before thrombolytic

| Patient Name | IVIG treatment? | Date of 1st IVIG treatment? | 2nd IVIG treatment? | Date of 2nd IVIG treatment | Other acute immune meds | Aspirin prior to thrombus | Coumadin prior to thrombus | Lovenox/ heparin prior to thrombus |
|---|---|---|---|---|---|---|---|---|
| Patient 1 | Yes | 03/25/06 | Yes | 4/13/06 | Coumadin, aspirin | Yes | Yes | no |
| Patient 2 | Yes | 11/30/06 | Yes | 12/03/06 | Aspirin, Remicade | Yes | No | No |
| Patient 3 | Yes | 10/16/12 | No | N/A | Aspirin, Heparin | Yes | No | Yes |
| Patient 4 | Yes | 12/06/12 | No | N/A | Aspirin | Yes | No | No |
| Patient 5 | Yes | 07/08/13 | Yes | 7/10/13 | Remicade, Coumadin, Aspirin | Yes | Yes | No |
| Patient 6 | Yes | 05/11/17 | No | N/A | Aspirin, Heparin | Yes | No | Yes |

Table 4. Thrombolytic type and dosage

| Patient Name | Date thrombus identified | Date of thrombolytic | Which thrombolytic | thrombolytic dose |
|---|---|---|---|---|
| Patient 1 | 04/18/06 | 04/23/06 | Heparin, abciximab, tPA | .25 mg/kg, infusion of .125 mcg/kg/min for 12 hours, .25 mg/kg/min for 6 hours |
| Patient 2 | 01/01/07 | 01/02/07 | tPA, heparin | .125 mg/kg, .25 mg/kg/min for 3 hours, then for 2 hours |
| Patient 3 | 10/16/12 | 10/16/12 | tPA, Abciximab, heparin | .5 mg/kg/min for 3 hours, .125 mcg/kg/min for 12 hours, 32 units/kg/hour |
| Patient 4 | 02/04/13 | 02/04/13 | tPa, Abciximab, Ceftriaxone | 25 mg/kg/min for 9 hours, 37.5 mcg/kg/hr |
| Patient 5 | 09/25/14 | 09/25/14 | tPA, Heparin, | .5 mg/kg/hr Iv for 6, 10 mcg/kg/hr during tPA |
| Patient 6 | 05/25/17 | 05/26/17 | tPA, Heparin | .5 mg/kg, 10 u/kg/hr |

Table 5. Thrombolytic Doses and Adverse Effects

| Patient Name | # of thrombolytic doses | adverse events from thrombolytic? | bleeding event from thrombolytic? |
|---|---|---|---|
| Patient 1 | 2 | No | No |
| Patient 2 | 3 | No | No |
| Patient 3 | 4 | No | No |
| Patient 4 | 2 | No | No |
| Patient 5 | 3 | No | No |
| Patient 6 | 4 | No | No |

Table 6. Aneurysm Size and Z-Scores before Thrombus

| Patient Name | max size of LAD (mm) | max size of LAD zscore | max size of proximal RCA (mm) | max size of prox RCA z-score |
|---|---|---|---|---|
| Patient 1 | 5.4 | 17.58 | 7.1 | 18.86 |
| Patient 2 | 6.4 | 18.2 | 6.6 | 14.7 |
| Patient 3 | 8.8 | 22.5 | 8.3 | 17.2 |
| Patient 4 | 14 | 16.5 | 16 | 18.7 |
| Patient 5 | 18.2 | 46 | 20.3 | 42.88 |
| Patient 6 | 6.7 | 11.8 | 9.7 | 19.7 |

Table 7. Aneurysm Size and Z-Score at Thrombus Formation

| Patient Name | size of LAD (mm) at thrombus | size of LAD zscore at thrombs | size of proximal RCA (mm) at thrombus | size of prox RCA z-score at thrombus | size of thrombus at diagnosis |
|---|---|---|---|---|---|
| Patient 1 | 5.4 | 17.58 | 7.1 | 18.86 | 4.5 mm |
| Patient 2 | 6 | 18.2 | 5.2 | 14.7 | 5.2 mm |
| Patient 3 | 8.8 | 22.5 | 8.3 | 17.2 | 4.12 |
| Patient 4 | 14 | 16.5 | 16 | 18.7 | 1.4 mm x 2.6 mm |
| Patient 5 | 18.2 | 46 | 20.3 | 42.88 | 1.6 mm x 1.8 mm |
| Patient 6 | 6.7 | 20 | 9.7 | 21 | 2.3 mm x 3.1 mm |

Table 8. Thrombus size after Thrombolytic and Adverse Effects

| Patient Name | Thrombus size over 1 week post thrombolytic | Myocardial Infarction? | Death? | Heart Transplant? | CABG? | Percutaneous coronary intervention? |
|---|---|---|---|---|---|---|
| Patient 1 | 2.9 mm | No | No | No | No | No |
| Patient 2 | 4.2 mm | No | No | No | no | No |
| Patient 3 | 1.7 mm | No | No | No | No | No |
| Patient 4 | 1 mm | No | No | No | No | No |
| Patient 5 | .8 mm | no | no | no | no | no |
| Patient 6 | .9 mm | No | no | no | no | no |

*Table 2. Demographics*

In this study, there were a total of 6 patients, 4 male (66%) and 2 (33%) female. There were 5 Caucasian patients (83%), and one African American patient (17%). The mean age of the patients at KD diagnosis was 4.41 years old.

Table 3. Medication administered before thrombolytic

All six patients included in this study received at least one IVIG treatment as well as aspirin. Three out of the six (50%) patients in the study did not receive another IVIG treatment. Acute medication was given to all patients between KD diagnosis and intravenous thrombolytic therapy. These medications include aspirin, coumadin, heparin, and lovenox. Two patients received heparin before thrombolytic, two patients received coumadin, and two patients received remicade.

*Table 4. Thrombolytic type and dosage*

All patients in this study received tPA, along with another type of thrombolytic. All thrombolytic drugs were administered intravenously for a specific duration of time. Duration of thrombolytic was dependent upon the patient's needs. Thrombolytic was administered aground 1-3 days after identification of the thrombus. Five patients received heparin along with tPA, three patients received abciximab as a adjunctive therapy, and one patient received ceftriaxone.

*Table 5. Thrombolytic Doses and Adverse Effects*

The average patient received three rounds of thrombolytic therapy, with none of the patients having any adverse events or bleeding due to thrombolytic intervention.

*Table 6. Aneurysm Size and Z-Scores before Thrombus*

Every patient included in this study were experiencing aneurysms in both the left anterior descending artery (LAD) and the right coronary artery (RCA). The mean aneurysm size in the proximal LAD was 9.9 mm, with an average Z-score of +22.1. The mean aneurysm size of the proximal RCA was 11.3 mm, with an average Z-score of +22.

*Table 7. Aneurysm Size and Z-Score at Thrombus Formation*

At the formation of the thrombus, the mean aneurysm size in the proximal LAD was 9.9 mm, with an average Z-score of +23.5. The mean aneurysm size of the proximal RCA was 11.3 mm, with an average Z-score of +22.22. The mean size of the thrombus was 4.58 mm.

*Table 8. Thrombus size after Thrombolytic and Adverse Effects*

In the seven days after thrombolytic treatment, the average reduction of the thrombus was 2.5 mm. None of the patients experienced any adverse cardiac events such as myocardial infarction, coronary artery bypass graft, heart transplant, percutaneous coronary intervention, or death.

The data does not support our null hypothesis that Intravenous thrombolytic therapy will not be effective in relieving the CA thrombus. The data supports our hypotheses that thrombolytic treatment would lead to an earlier resolution of coronary artery thrombosis, and that thrombolytic therapy is associated with an acceptable safety profile.

## *5.0 Conclusion 5.1 Major Findings*

In this observational retrospective case series of thrombolytic therapy in KD, there are two inferences can be made from this study. It can be inferred that thrombolytic therapy leads to earlier resolution of coronary artery thrombosis in KD compared to conservative anticoagulation management. Also, it can be inferred that thrombolytic therapy is associated with an acceptable safety profile in relieving coronary artery blood-flow.

### *5.2 Discussion*

This study was directly aligned with the aim of the National Heart Lung and Blood Institute's goal to "promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives." This study confirms the findings by Harada in 2013[2], Abe in 1992[4], Tsuda in 2007[21], and Burns in 2000[33]. In reference to tables 4 and 7, the number of thrombolytic doses did not have a significant effect on the decrease of the thrombus. Also, the number of IVIG treatments underwent by each patient do not have a significant effect on decreasing the burden of the thrombus. The present results additionally confirmed that thrombolytic therapy is more

effective as the time from thrombus formation until the start of treatment becomes shorter, as was already well known. When the response rate was analyzed by treatment method, the response rate to thrombolytics was high even when considerable time (≥1 week) had elapsed since thrombus formation. Because of the small sample size, no definite conclusions about the efficacy of thrombolytics can be drawn, either alone or combined with another therapy, but all responders to thrombolytics, both alone and combined, received treatment within several hours after thrombus formation. Despite these results, it is difficult to conclude that thrombolytics are not effective in cases in which several days or even a week or more has elapsed since thrombus formation. It is important to not rule out the possibility that even slight thrombolysis achieved by thrombolytics on the thrombus surface later enhances responses to thrombolytic therapy.

### *5.3 Limitations*

The main study limitations are the retrospective nature of the study, which makes it susceptible to information biases and missing data, and the small sample size. Another limitation was that only descriptive statistics were performed.

### *5.4 Future Research*

Overall this data shows that there is still much to be investigated in the future regarding thrombolytic therapy in KD. Future research can include a larger sample size, with more centers to get data from. This data opens up new doors for research into thrombolytic therapy in the future, and other primary adjunctive therapies to help relieve CAA and thrombus burden.

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