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Original Article

Paediatrics Section

Impact of Recombinant Tissue Plasminogen Activator Therapy (rtPA) on The Short Term Outcome of Neonatal Thrombosis-A Retrospective Study

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ABSTRACT

Introduction: The incidence of clinically apparent neonatal thrombus varies from 5.1 per 1 lakh live births to 2.4 per thousand newborns admitted to neonatal intensive care unit. Well established protocols for the use of fibrinolytic agents like Recombinant Tissue Plasminogen Activator (rtPA) are present for adults, but the same cannot be said for neonates.

Aim: To study the effectiveness of rtPA therapy in the treatment of neonatal thrombosis in our centre.

Materials and Methods: A retrospective study of neonates diagnosed to have venous, atrial or arterial thrombosis was done for a period of seven years using G HEALTH data base systems. All neonates were treated with rtPA. A total of three doses were given 24 hours apart for the next 72 hours; followed by Enoxaparin, given for three months subcutaneously. Repeat scan was done at 72 hours, before discharge, after one month and three months after starting treatment. Treatment outcome was defined as partial or complete thrombus resolution or no change following treatment. Statistical analysis using SPSS 17.0 analysed median and interquartile range of the data.

Results: Eight patients were diagnosed with neonatal thrombosis. Complete thrombosis resolution was documented in six patients while partial thrombus resolution was found in two cases. The median follow up was 13 months.

Conclusion: Treatment for neonatal thrombus remains controversial and no set protocols has been established in management of neonatal thrombus. There is very little experience with fibrinolytic treatment in neonatal period.

Keywords: Alteplase, Enoxaparin, Fibrinolysis

INTRODUCTION

The haemostatic system in babies is immature, due to which there is a higher risk for thrombus formation in the neonatal period than in childhood. They also have decreased ability to generate thrombin. [1] In the critically ill neonate, additional risk factors may contribute to the development of thrombus. [2]

The safety and efficacy of rtPA treatment in neonates has not been studied by randomised controlled trials [3]. Thrombosis occurs more frequently in the neonatal period than any other age in childhood. Thrombosis and thromboembolic phenomenon in neonates widely varies between 2.4 per 1000 neonatal admissions to 5.1 per 100,000 live births. [3] However, a recent review [4] suggested that a much higher incidence of 6.8 per 1000 NICU admissions may be seen depending on how aggressively thrombosis is screened for in the NICUs. Umbilical Venous Catheters (UVCs) and peripherally inserted CVCs which are routinely used in all NICUs have a significant risk of development of thrombosis. [3] Earlier studies [5-7] of autopsies of neonates who have died with UVC in situ showed 20-65% of the babies had microscopic evidence of thromboembolism. [3]

Thrombolytic agents are commonly used for the treatment of neonatal thrombosis. Recombinant Tissue Plasminogen Activator (rtPA) has a short half-life and localised fibrinolytic activity and hence is the preferred option, but the response varies widely. Neonates have reduced level of plasminogen and decreased production of plasmin which probably explains the varied clinical response while treating. [8] Action of TPA is characterised by a locally potent effect, which helps minimise the occurrence of systemic side effects. rtPA has a rapid curative effect on thrombi, which is a great benefit as it can minimise the incidence of acute tissue and organ necrosis.[9] rtPA has been

effectively used to treat catheter-related intracardiac thrombus and vena cava inferior thrombus.[10,11]

Decision making regarding therapeutic strategies is a challenge for the intensive care physician as the clinical significance of neonatal thrombosis varies from asymptomatic incidents to life- or limb-threatening events; moreover, appropriate evidence-based treatment algorithms are lacking. [12]We present our experience with the management of eight cases of neonatal thrombosis with rtPA.

The aim was to study the effectiveness of rtPA therapy in the treatment of neonatal thrombosis in our centre. The objective was to study the time taken for complete clot resolution after treatment with rtPA.

MATERIALS AND METHODS

A retrospective study of all neonates who were admitted to A.J. Hospital and Research Centre neonatal intensive care unit (NICU) and diagnosed to have venous, atrial or arterial thrombosis was conducted after taking ethical committee clearance from the institutional Ethics Committee (AJEC/Rev/27/2017-18). Patients were identified using G-HEALTH Enterprise version 3.0 (Gestalt Technologies Pvt. Ltd., Bangalore) database systems which maintains a database of hospital in patients and their records for a ten year period. The patients were traced from the hospital pharmacy database which is dedicated for the NICU and further details of treatment and course in the hospital was collected by chart review. Written informed consent was obtained. All newborns diagnosed and treated between August 2011 and January 2018 were included in the study. The first newborn was diagnosed in August 2011 and the last one was diagnosed in December 2017.

Inclusion Criteria: Amongst all neonates admitted to the NICU, those who were diagnosed to have atrial, arterial or venous thrombus either by 2D echocardiography (2D ECHO) or ultrasound abdomen (USG) and later treated with rtPA were included in the study. Exclusion criteria were newborns whose complete data including follow up were not available or those lost to follow up. The total number of newborns admitted during this time period was 4213.

In the period analysed, a total of eight newborns were identified with thrombosis. Data collected included patient birth weight, gestational age, gender, placement of indwelling catheters, protocol followed for management of thrombosis and any recorded adverse effects.

Platelet count, liver function including aPTT, PT, INR reports were recorded along with the reports of cranial ultrasound and doppler ultrasound. The 2 DECHO was done for all the patients by the same paediatric cardiologist. Serum fibrinogen, protein C, protein S and plasminogen levels were not analysed in any of these patients probably due to financial reasons.

For all the patients, the same treatment protocol was followed which included the dose, route of administration, and monitoring. The treatment was initiated immediately on diagnosis. 0.3 mg/kg of rtPA (Inj. Alteplase), was given as loading dose as an intravenous infusion over one hour followed immediately by maintenance infusion of 0.1 to 0.3 mg/kg/dose infusion over 12 hours. A total of three doses of maintenance infusion of rtPA along with heparin infusion of dose 25 IU/Kg was administered over the next 72 hours. Repeat USG or 2D ECHO was done after 72 hours to see the resolution of the thrombus. Low molecular weight heparin (Enoxaparin) was given for three months at a dose of 1.5 mg/kg/dose twice a day subcutaneously to all the patients irrespective of their thrombus status at 72 hours.

Review USG and 2 DECHO was done after four weeks and 12 weeks after starting treatment.

Treatment outcome was defined as partial thrombus resolution, complete thrombus resolution or no change following treatment and was assessed using imaging results of 2D ECHO or USG/Doppler after 72 hours of treatment with rtPA. Any immediate adverse effects were monitored for.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS software version 17.0. Median and interquartile range was calculated for the demographic data as well as the time taken for clot lysis.

RESULTS

A total of eight newborns were identified with neonatal thrombosis during the period of the study. The mean gestational age of the study cohort was 37 weeks and 5 days. Two babies included were late preterms as shown [Table/Fig-1]. Majority (62.5%) were male although it was not statistically significant. The mean birth weight was 2.81kgs. Median age at diagnosis of the baby was 8.5 days (IQR 5.5 – 11.5). Except for one, all patients with venous thrombosis had an umbilical venous line and two patients with arterial thrombosis had an umbilical arterial line inserted previously. The median number of days of indwelling catheter was found to be 7.5 days [Table/Fig-2]. Additional co-morbidities like birth asphyxia and sepsis were noted in the patients with arterial thrombus. Sepsis occurred in two patients with arterial thrombus during treatment which may or may not have correlation to thrombus treatment. Six of our patients were diagnosed to have venous or right atrial thrombus by 2D ECHO and two patients were diagnosed to have arterial thrombus by USG abdomen. One patient with arterial thrombosis had a thrombus is the descending aorta extending in to the left renal artery causing renal artery stenosis. Complete thrombosis resolution was documented in six patients (75%) with venous and atrial thrombosis after three doses of rtPA within 72 hours. Partial thrombus resolution was found in two patients with arterial thrombosis after treatment with rtPA at the scan done

Patient No.	Gestational age	Sex	Birth weight (Kg)	Co-morbidities/ Uvc/Uac	Age at diagnosis (Days)
1.	38 weeks+2 days	Male	2.8	None	5
2.	39 weeks+4 days	Male	3.4	None	10
3.	36 weeks	Male	2.3	Preterm	6
4.	37 weeks+5 days	Male	2.9	None	5
5.	40 weeks+2 days	Female	3.2	Birth asphyxia, sepsis	18
6.	34 weeks+3 days	Female	2.2	Preterm	8
7.	37 weeks+2 days	Male	2.6	None	13
8.	38 weeks+5 days	Female	3.1	Sepsis	9

[Table/Fig-1]: Demographic Data.

Patient No.	Indwelling catheter	No. of days of indwelling catheter
1.	Umbilical venous catheter	4
2.	Umbilical venous catheter	7
3.	None	-
4.	Umbilical venous catheter	6
5.	Umbilical arterial catheter	5
6.	Umbilical venous catheter	11
7.	Umbilical venous catheter	8
8.	Umbilical artertial catheter	9

[Table/Fig-2]: Number of days of indwelling catheter.

at 72 hours. Complete thrombus resolution was seen in these two patients on their follow up at four weeks [Table/Fig-3]. One preterm had a Grade 2 intracranial bleed after the third dose of rtPA which was diagnosed by a cranial ultrasound. None of the patients had other known complications like allergic reactions to drugs, severe bleeding or purpura fulminans during this period. The median follow up was 13 months, during which no adverse effects were noticed.

DISCUSSION

The incidence of thrombus is rising due to extensive use of intravascular catheters [2], increased availability of diagnostic imaging investigations and consequentially neonates surviving sepsis. A study done in 2007 by Turebylu et al revealed 21.4% of neonates with UVCs had thrombus formation, most of which were in the inferior vena cava (IVC). [13] These thrombi can cause life threatening complications which need prompt diagnosis and treatment. However, treatment protocol to manage them is not yet established. [14] Thrombolytic therapy for neonatal thrombosis derived from uncontrolled studies,

Patient No.	Site of thrombus	Thrombus Status at 72 hours	Time for complete resolution	Follow up time (months)
1.	Inferior vena cava below diaphragm	Complete resolution	Within 72 hours	24 months
2.	Tip of UVC	Complete resolution	Within 72 hours	19 months
3.	Right atrium	Complete resolution	Within 72 hours	15 months
4.	Interatrial septum	Complete resolution	Within 72 hours	10 months
5.	Abdominal aorta below renal artery	Partial resolution	Within 4 weeks	14 months
6.	Tip of UVC	Complete resolution	Within 72 hours	8 months
7.	Tip of UVC	Complete resolution	Within 72 hours	10 months
8.	Left renal artery, Abdominal aorta, Left iliac artery	Partial resolution	Within 4 weeks	4 months

[Table/Fig-3]: Characteristics of thrombus and follow up.

extrapolation from adult and paediatric data, small case series, cohort studies or expert opinion. [3]

Thrombi can occur spontaneously due to an underlying predisposing risk factor [8], which can be dehydration, sepsis, prematurity, birth asphyxia, polycythemia, chorioamnionitis, intra-uterine growth retardation, infants undergoing repair for congenital heart disease and thrombophilias. [14] Intracardiac or great vessel thrombi may lead to life threatening situations. [15-17]

There was a slight preponderance of thrombosis in males which was not considered to be significant as shown by Tootoonchi et al. He also showed that a higher age at diagnosis was protective for neonatal thrombosis [18], however, there was no such relation seen in our study.

Management options in neonatal thrombosis range from expectant management to thrombolytic agents and surgery. No effective randomised controlled trials have been done to study the effectiveness of rtPA in neonates and it so may be reckoned that none might ever be performed because the risk of withholding such treatment may far outweigh the benefit obtained from a controlled trial. [3] All our patients were treated for the thrombosis irrespective of their clinical symptoms due to the possibility of embolization of the thrombus.

Several studies [4,5,15],suggest varied doses of rtPA for successful lysis of neonatal thrombosis. An observation by Erdinc et al published in 2011 of a preterm neonate weighing 940 grams with intra-arterial thrombus showed successful treatment with alteplase infusion at 0.2 mg/kg/hr.[9]Hartmann et al used an

initial bolus of 0.7 mg/kg/hour followed by intravenous infusion of 0.2 mg/kg/hour for a period of 1 – 5 days. This succeeded in lysing the clot in 94% of the cases. [19] In a study done by El-Segaier et al, rtPA was given at dose of 0.5 mg/kg/hour for six hours and then continued at 0.25 mg/kg/hour until complete clot lysis or five days whichever was sooner. They found that most patients required rtPA only for a period of three days which was the period that we gave rtPA in our cases with 75% complete clot lysis. However, longer lysis time was seen in the larger vessel thrombosis in our study as opposed to intracardiac thrombus which was reported by El-Segaier et al. [8]

A longer duration of therapy with alteplase was found to be associated with bleeding episodes in a case series presented by Al-Jazairi AS et al., However, no such adverse effects were noted in our neonates. Only one preterm had an intracranial bleed after the third dose of alteplase, however evidence suggests preterms to be at higher risk of bleeding events. [20] Higher dose of rtPA is not associated with better action, instead it is associated with higher risk of bleeding. [8]

The safety and efficacy of rtPA therapy in neonates have only been studied and reported as case reports or case series and few cohort studies. [16,21-23]

A study by Knöfler R et al., that included 20 children (age between 1 day and 16 years) with thrombosis reported that 11 patients treated with rtPA had a complete response.[24] Majority of the studies have shown complete or partial clot lysis similar to the results in our study which showed an immediate success rate with alteplase administration of 80%, of which 100% resolution was observed with venous thrombus whereas partial resolution was observed in arterial thrombus after 72 hours. In the patients with arterial thrombosis, complete resolution was seen at their four weeks follow up.

Piersigilli F et al., has published his experience with enoxaparin in a retrospective study in 2013 stating that of the 19 neonates diagnosed to have thrombus, newborns who received enoxaparin of dose 175 IU/KG SC BD achieved therapeutic anti factor Xa level earlier than those who received recommended 150 IU/KG SC every 12 hours without major or minor bleeding [25]. Michaels LA et al., did a study in 2004 and published their experience with 10 premature neonates with mean patient weight at diagnosis was 1215gm was given enoxaparin of mean dose 2.2 mg/kg per 12 hours. Clot resolution was seen in eight premature neonates whereas two neonates died due to thrombo-embolic complications [26].

LIMITATION

The sample size in our study was small. Serum fibrinogen levels, protein C and protein S, serum plasminogen values were not assessed in our patients due to financial reasons.

CONCLUSION

There are established protocols for fibrinolytic treatment in adults but treatment for neonatal thrombus remains controversial and no set protocols has been established in management of neonatal thrombus. There is very little experience with fibrinolytic treatment in neonatal period. Randomised double blinded studies need to be conducted to establish guidelines for the same.

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