Original Article

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Neonatal Thrombosis: Incidence and Risk Factors in a Tertiary Care Hospital in Iran

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Abstract

Background: Neonatal thrombosis is one of the most important challenges among patients admitted in Neonatal Intensive Care Unit (NICU), which can lead to an asymptomatic condition, limb loss or even death. This study was performed to determine the incidence and risk factors of neonatal thrombosis in a tertiary care hospital in Tehran, Iran.

Material and Methods: In this historical cohort, all neonates admitted to Ali-Asghar children's hospital, Tehran, from Sep 2014 till Mar 2015 were enrolled. If thrombosis happened and proved with Color Doppler ultrasonography, the data about type and place of thrombosis, occurrence of complications, recurrence of thrombosis, and the swelling of the extremity distal to the thrombosis area were collected. The statistical significant level was set less than 0.05. SPSS (version 16) was used for data analysis.

Results: The neonatal thrombosis incidence was 2.87% (14 cases out of 489). Most of cases (13, 92.9%) had venous thrombosis and one case (7.1%) had arterial thrombosis. Femoral vein thrombosis following catheter insertion has occurred in 9 cases (64.2%) of thrombosis. In multivariate analysis with multiple regression, a statistical significant relation was found between thrombosis and neonatal age at admission ($P < 0.0001$), using central vein catheter ($P < 0.0001$), history of exchange transfusion ($P < 0.015$), and exclusive breast feeding ($P < 0.006$) suggesting that lower age at admission, using of a central vein catheter or positive history of exchange transfusion was an independent risk factor for thrombosis; using exclusive breast feeding had a protective effect on thrombosis.

Conclusion: Most of our findings are in agreement with the results of other studies. Some interesting results included the significant relation between thrombosis and neonatal age at admission, history of exchange transfusion or exclusive breast feeding.

Keywords: Incidence, Neonatal, Risk Factor, Thrombosis

Introduction

It is known that among children, newborns are the most susceptible groups for thrombosis and its life-threatening complications (1). Reduction of anticoagulant factors activity including antithrombin III, protein C and protein S as well as fibrinolytic factors due to low level of serum plasminogen make the neonates highly prone to thrombosis (2-3). Among neonates, premature ones(2,4,5), those who are critically ill affected by asphyxia, sepsis, dehydration (1,4,5,6), cyanotic congenital heart disease(7), thrombocytopenia (1) or the babies of diabetic mothers (4), using of central vein catheter (2,4,5,8-15,) or umbilical vein catheter(14,15) and males (4,5) are at the highest risk. Despite some studies mentioned relatively low incidence of thrombosis in Neonatal Intensive Care Unit (NICU) (12), it seems that nowadays, the figures are increasing especially in developing countries; this problem is probably due to a great number of admissions in NICU, usage of invasive and complex therapeutic interventions, necessity of using of mechanical ventilation and performing major life saving operations for correcting major congenital anomalies as well as handling their complications. These challenges

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mostly result in long period of the newborn staying in NICU, which in turn requires accessing to IntraVenous (IV) lines or doing cutdowns, maintaining IV serums, antibiotics or even using Total Parentral Nutrition (TPN) as well as prescribing different blood products during the neonate's admission. Although, some factors implicated as the most important risk factors for occurring of neonatal thrombosis, most of the studies have been conducted in developed countries and there are only a few reports from developing countries if there is any. The reasons for this difference are diverse; however, the major one is probably the difficulty of conducting multicenter studies in such countries. Moreover, there is no data about the incidence and risk factors of neonatal thrombosis in Iran. Ali-Asghar children's hospital is one of the oldest and the most famous centers in neonatal practice and it includes one of the oldest NICUs in the country. Considering the mean admission number of neonates in the hospital is more than 1000 cases annually, it seems that determining the incidence and risk factors of thrombosis in the newborns can serve as a good estimate of the event in Iran.

Materials and Methods

In this historical cohort, all neonates admitted to nursery ward or NICU of Ali-Asghar children's hospital, from Sep 2014 till Mar 2015 were included. Inclusion criteria included admission in the nursery ward or NICU of the hospital during the studied period of time. There was no exclusion criterion. Using a check list, data of the neonates were collected from their records. The recorded data included neonate's demographic data such as age, sex, birth weight, gestational age, as well as the history of the maternal diabetes (overt as well as gestational diabetes), neonate's thrombocytopenia, polycytemia, hypovolemia, exchange transfusion, receiving blood products (such as packed cell, Fresh frozen plasma (FFP), platelets), receiving IV serums or antibiotics, using peripheral or central IV line, umbilical vein or artery catheter insertion, using mechanical ventilator, and/ or prophylactic heparin, history of neonate's major operation and/or critical illness, neonatal death during admission and feeding type. Thrombosis occurrence documented by a portable Color Doppler ultrasonography (Sonosite M-turbo, USA) in the suspected cases according to their clinical manifestations. For neonates with thrombosis, the data were collected about the age of thrombosis onset, type and place of thrombosis, occurrence of complications, thrombosis recurrence and the swelling of the extremity distal to the thrombosis area if there was any. All the central vein catheters were provided by the hospital from an internationally approved Brand made by the same manufacturer (Arterial catheterization set. Arrow international Imc. IDA business and technology park. Athlone. Ireland). The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences. SPSS (version 16) was used for data analysis. To compare the means, T-test was run. To compare categorical data, Qui square or Fisher exact test was applied. Multiple regression analysis was used for comparing more than one risk factor. P.Value < 0.05 was considered statistically significant.

Results

During the study, 489 neonates were admitted to the hospital included 275 (56.2%) male and 214 (43.8%) female. The mean age of participants was 8.65 days with Standard Deviation (SD) of 11.82 days (Range: 1-80 days). Overall, the frequency of prematurity or low birth weight among neonates was 140 (28.6%) or 133(27.2%), respectively. History of maternal diabetes was positive in 30 of the mothers (6.1%). Most of the neonates used exclusive breast feeding (367, 75%).The frequency of critical illness was high among the neonates (208, 42.5%). Besides,

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312 neonates (63%) had peripheral vein access and 310 neonates (63%) used intravenous antibiotics. The frequency of receiving at least one blood product was high among the neonates (110, 22.5%). History of major operation was positive in 72 neonates (14.7%).Overall, using mechanical ventilation or inserting a central vein line was performed in 76 neonates (15.5%) and 53 neonates (10.8%) respectively. History of thrombocytopenia during admission was positive in 30 neonates (6.1%). Overall, using an umbilical vein catheter (19, 4%) or performing exchange transfusion (6, 1.2%) was not common. None of the neonates involved with polycytemia, hypovolemia or used umbilical artery catheter. The mean age at admission in neonates with or without thrombosis was 20 days or 8 days, respectively. In a nutshell, the mean gestational age or birth weight in neonates with thrombosis was lower than other neonates (33 weeks and 1890 gram versus 36 weeks and 2853 gram respectively). Furthermore, the mean number of admission days in neonates with thrombosis was higher than other neonates (27 days versus 9 days). Moreover, the cases with thrombosis experienced much more number of venipuncture during their admission (19 times versus 6 times). The study revealed that the cases received more number of blood products during their admission in comparison with other neonates; these blood products included FFP (2 times versus 0.2 time), platelet (0.8 time versus 0.5 time) and packed cell (4 times versus 0.4 time).

The frequency distribution and percent of neonatal thrombosis by neonatal characteristics is shown in Table I. The distribution of neonatal quantitative characteristics by thrombosis is shown in Table II. The neonatal thrombosis incidence was 2.87% (14 cases out of 489). The cases included 9 (64.21%) female and 5 (35.71%) male. The mean age of cases at thrombosis onset was 31 days (SD 21.7 days). The mean days of admission before occurrence of thrombosis were 10 days (SD 7.5 days). Most of the cases had central vein catheter before thrombosis onset (13 cases, 92.8%) and the mean days of catheter insertion before thrombosis occurrence was 7 days (SD 4.2 days). Generally, the incidence of thrombosis was higher in females, older, premature and/ or low birth weight neonates or those who had diabetic mothers, thrombocytopenia, critical illness, and/or exchange transfusion, received blood products, IV serums and antibiotics, used peripheral or central vein catheter, umbilical vein catheter, mechanical ventilator, not used exclusive breast feeding or undergone a major operation. Despite significant relation between neonatal thrombosis and most of the neonatal characteristics in univariate analysis (Table I and Table II), multiple regression analysis revealed that only the relation between thrombosis and neonatal age at admission ($P < 0.0001$), history of exchange transfusion ($P < 0.015$), using of central vein catheter ($P < 0.0001$) or exclusive breast feeding ($P < 0.006$) was statistically significant (Table III).

Overall, the incidence of thrombosis was 2.87% (14 cases) in the study. The mean age of the cases was 20.29 days (SD: 23.22) with range 1-56 days.

Regarding the type of thrombosis, most of our cases (13, 92.9%) had venous thrombosis (one case (7.1%) had arterial thrombosis). According to the thrombosis place, thrombosis occurred following right or left femoral vein catheter insertion in 8 cases (57.1%) and 1 case (7.1%), respectively. Other places of thrombosis included the following: A case (7.1%) involved with both common Iliac vein and right external Iliac vein thrombosis following right femoral vein catheter insertion; A case (7.1%) of left renal vein thrombosis was detected in a neonate with umbilical vein catheter; Brachial vein thrombosis occurred in one case (7.1%) following venipuncture of right upper extremity and in other case (7.1%)

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following DIC; There was only a case of Brachial artery thrombosis presenting with left upper extremity gangrene, left ear and left foot as well as scalp echimosis following Ileostomia (has discharged from hospital 2 days before readmission). Extremity swelling distal to the catheter insertion place observed merely following femoral vein catheter insertion in 9 cases (64.2%). No case of thrombosis recurrence or complication detected in the studied cases.

All of the cases (14 cases) involved with at least a critical illness. These critical illnesses included 1 case of severe asphyxia, 1 case of neuroblastoma, 1 case of congenital pneumonia, 1 case of Respiratory Distress Syndrome (RDS), 2 cases of Necrotizing Entro Colitis (NEC), 2 cases of intestinal perforation and peritonitis following intestinal atresia, 1 case of esophageal atresia with imperforated anus, 1 case of esophageal atresia with TE fistula, 2 cases of Ilium atresia and 2 cases of neonatal sepsis.

Besides, no case of death occurred as a complication of thrombosis. High percent of cases (6 cases, 44.4%) died during their staying in the hospital because of their primary critical illnesses or their complications; they included 3 cases following septicemia induced by intestinal perforation or NEC, 1 case following both esophageal atresia and imperforated anus operation, one case following congenital pneumonia and 1 case induced by pulmonary infection following esophageal atresia and TE fistula operation. Overall, 8 cases (55.6%) survived and discharged from hospital without any problem.

Table I: Distribution of frequency and percent of Neonatal thrombosis by neonatal characteristics

Neonatal characteristics:	Thrombosis Yes Number (%)	Thrombosis No Number (%)	P.Value	Neonatal characteristics	Thrombosis Yes Number (%)	Thrombosis No Number (%)	P.Value
sex			**no significant**	**using central vein**			**<0.001**
male	5 (1.8)	270 (98.2)		yes	13 (24.5)	40 (87)	
female	9 (4.2)	205 (95.8)		no	1 (0.2)	435 (99.8)	
gestational age			**<0.001**	**using umbilical vein**			**no significant**
<37 weeks	10 (7)	130 (93)		yes	1 (5.3)	18 (94.7)	
=> 37 weeks	4 (1.1)	345 (98.9)		no	13 (2.8)	457 (97.2)	
birth weight			**<0.004**	**major operation**			**<0.001**
<2500	9 (6.8)	124 (93.7)		yes	7 (9.7)	65 (92.3)	
=>2500	5 (1.4)	351 (98.6)		no	7 (1.7)	410 (98.3)	
maternal diabetes			**no significant**	**iv antibiotic**			**<0.003**
yes	2 (6.7)	28 (93.3)		yes	14 (4.5)	296 (95.5)	
no	12 (2.6)	447 (97.3)		no	0 (0)	159 (100)	
thrombocytopenia			**<0.001**	**mechanical ventilation**			**<0.001**
yes	6 (20)	24 (80)		yes	10 (13.2)	66 (86.8)	
no	8 (1.7)	451 (98.3)		no	4 (1)	409 (99)	
blood products			**no applicable**	**exclusive breast feeding**			**<0.05**
yes	14 (12.7)	96 (87.3)		yes	7 (1.9)	360 (98.1)	
no	0 (0)	379 (100)		no	7 (5.7)	115 (94.3)	
exchange transfusion			**<0.001**				
yes	1 (16.7)	5 (83.2)					
no	13 (2.7)	470 (97.3)					
critical illness			**<0.001**				
yes	14 (6.7)	194 (93.3)					
no	0 (0)	281 (100)					
using peripheral vein			**<0.003**				
yes	14 (4.5)	298 (95.5)					
no	0 (0)	187 (100)					

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Table II. Distribution of Neonatal quantitative characteristics by thrombosis

Neonatal Characteristics	Thrombosis					
	Yes		No			
	Mean	SD	Mean	SD	%95 confidence interval	P.Value
age (day)	20.2	23.2	8.3	11.2	5/76-18/19	<0.001
gestational age(wks)	33.1	4.3	36.8	2.9	-5/31- -2/19	<0.001
birth weight(g)	1890	968	2853	791	-1387/05- -537/97	<0.001
days of admission	27	16	9	12	11/44- 24/53	<0.001
venipuncture number	19	8.9	6	6.8	9/67- 16/96	<0.001
FFp	2.1	2.5	0.2	0.9	1/43- 2/48	<0.001
platelet	0.8	0.97	0.5	0.3	0/55- 0/91	<0.001
packed cell number	4	2	0.4	1	3/00- 4/35	<0.001

Table III: Multiple regression analysis results for neonatal thrombosis by some of the neonatal characteristics

Variable	B	S.E	Wald	df	Sig.	Exp(B)	95.0% C.I. for EXP(B)	
							Upper	Lower
breast milk step1[a]	-2.304	0.832	7.665	1	0.006	0.100	0.020	0.510
age	-0.087	0.024	13.405	1	0.000	0.917	0.875	0.960
central vein line	5.002	1.035	23.364	1	0.000	148.769	19.570	1.131e3
exchange	4.275	1.759	5.9.4	1	0.015	71.878	2.286	2.260e3
constant	-7.964	3.730	4.559	1	0.033	0.000		

Discussion

The incidence rate of thrombosis in this study was 2.87%. This rate is similar to the rate in another study (14); however, it seems that this rate is high. One of the reasons for the high rate is probably due to a large number of the neonates affected by critical illnesses in the study (42.5%). Moreover, lots of the severely ill neonates referred to the hospital's NICU from other hospitals throughout the city as the unit is one of the few tertiary level NICUs in the area. As other studies have shown (1), this study also found out that the neonates with critical illnesses were the more frequent group who suffered from thrombosis (In fact all of the 14 cases involved by at least a critical illness). Other investigators did mention prematurity as well as low birth weight as serious risk factors for thrombosis (1-2, 4, 5, 10, 16); however, this study didn't confirm this finding. The variation between the statistical methods used for analysis probably could justify this difference. In contrary with other reports, no significant relation between thrombosis and neonatal thrombocytopenia was found (1). This discrepancy may be explained by low number of the neonates (overall 6.1%) involved with thrombocytopenia in the present study. It is noteworthy that like other studies, there was a remarkable percentage of inserting central vein catheters (10.8% in general) performed for the neonates. These lines mostly included femoral vein catheters and a few Jugular vein ones and unexpectedly, the rate of thrombosis was very high among the neonates used them (24.5%), that is very similar to the findings in other studies (2, 14,15,17). Actually, 80% of the thrombosis in the cases emerged following

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insertion of central vein catheter which is in support of the results of other reports (2, 8-10, 18-19). Some studies suggest central vein catheter as an important risk factor for neonatal thrombosis (1, 2, 4, 13). This finding has been documented by the present study too. Because of high risk of thrombosis occurrences following inserting umbilical vein catheter (14, 15), this practice is uncommon in the hospital's NICU and overall, only 3.9% of the neonates used an umbilical vein catheter. The occurrence of thrombosis in this group was very low (5.3%) opposite the reports of other investigations (10, 20). As some other studies have pointed out (21), there was no significant relation between thrombosis and using umbilical vein catheter. Evidence have shown that most of the neonatal thrombosis were venous ones (12, 17, 22); 93% of the cases of this study involved by venous thrombosis too. Other studies documented that prophylactic heparin just helped to maintain catheters open and didn't reduce the incidence of thrombosis (22, 23). Similarly, there was no recorded usage of prophylactic heparin in the neonates with central venous catheters admitted to this hospital, either. The reasons for this practice in the neonates was medical contraindications for using heparin included very low birth weight, septicemia, using mechanical ventilation, thrombocytopenia, etc. In all of the neonates with femoral venous thrombosis (69.4%), NICU personnel detected swelling extremity distal to the catheter insertion and then, a Color Doppler ultrasonography was ordered and approved thrombosis diagnosis. This event was considered as a common clinical sign for thrombosis by other studies too (10). As expected, using blood products such as packed cell, FFP or platelet, was very common in critically ill neonates admitted in NICU and it is considered one of the risk factors for thrombosis (10); however, the latter finding was not confirmed by the results of this study, probably because all of the cases used at least one blood product before thrombosis onset. Despite other reports mentioned significant relation between thrombosis and polycytemia or hypovolemia (1), none of the studied neonates had polycytemia or hypovolemia at the presentation. Therefore, this relation could not be evaluated. Although, most of the cases with thrombosis were females (64.4%), there was no significant relation between thrombosis and sex, like other studies (16). One of the interesting results found out in the study was significant relation between thrombosis and history of performing exchange transfusion in the neonate. Overall, 1.2% (6 neonates) of the studied neonates had an exchange transfusion and 7.1% of the cases (1 case) had the positive history. No record about this relation was found in other articles. Yet, another interesting finding in the study was the relation between thrombosis and the age of the neonate at the admission. The study showed that higher age of neonate at admission was a protective factor for neonatal thrombosis. This finding may be explained by some changes happened in hemostasis of anticoagulant factors, as well as antifibrinolytic factors of neonates with getting older. This subject needs to be approved by more accurate measurements of these factors especially during early months of life; though, no other articles referred to this relation before.

Generally, the rate of using exclusive breast feeding was high among the studied neonates (367, 75%) and 50% of the cases (7 cases) were exclusively breast fed during their admission before thrombosis onset. The percent of thrombosis occurrence was low in these neonates in comparison to the event in other neonates (1.9% versus 5.7%). Although using exclusive breast feeding was a significant protective factor for neonatal thrombosis in the study, the relation was not mentioned in other resources. Unfortunately, the death rate was very high in the cases (50%), which is much

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higher than the numbers have shown in other studies (2, 12-13). One of the reasons for this difference was the high percent of critical illnesses or their complications in the cases. Actually, 80% of the cases were affected by a systemic infection which was much more than the figures in other studies (12). This subject in turn was probably the result of a large number of referral cases included in the study.

Conclusion

In summary, the findings of this study were very similar to the results of other studies. However, further prospective multicenter cohort studies are recommended in order to assess the incidence and risk factors of neonatal thrombosis more accurately especially in developing countries which have their unique problems and challenges.

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Conflict of interest

Authors have no conflict of interest.

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