Türk Pediatri Arşivi
Turkish Archives of Pediatrics

Original Article / Özgün Araştırma

The danger awaiting premature babies: Portal vein thrombosis

Prematüreleri bekleyen tehlike: Portal ven trombozları

Salih Çağrı Çakır[1], Hilal Özkan[1], Bayram Ali Dorum[1], Nilgün Köksal[1], Pınar Kudretoğlu[2], Birol Baytan[3], Melike Sezgin[3], Adalet Meral Güneş[3]

[1]Division of Neonatology, Department of Pediatrics, Uludağ University Faculty of Medicine, Bursa, Turkey
[2]Department of Pediatrics, Uludağ University Faculty of Medicine, Bursa, Turkey
[3]Division of Pediatric Hematology, Department of Pediatrics, Uludağ University Faculty of Medicine, Bursa, Turkey

The known about this topic

Umbilical vein catheters may lead to portal vein thrombosis. Umbilical vein catheters inserted in the neonatal period are among the reasons for childhood portal hypertension.

Contribution of the study

Patients who have undergone umbilical vein catheter placement should be screened routinely using Doppler ultrasonography in terms of portal vein thrombosis without investigating any other risk factor. A significant portion of cases of portal vein thrombosis may require treatment according to Doppler ultrasonography findings and follow-up.

Abstract

Aim: Umbilical venous catheters are frequently used in the neonatal period. The incidence of umbilical venous catheter-related thrombosis is between 1.3% and 43% in ultrasound scans. This study aimed to determine the incidence and risk of portal vein thrombosis in patients who were hospitalized in the neonatal intensive care unit and underwent umbilical venous catheter insertion.

Material and Methods: Premature infants (≤32 gestational weeks) who were hospitalized in a Level III neonatal intensive care unit and underwent umbilical vein catheter placement between 2016 and 2018, were included in the study. The demographic data, clinical risk factors for thrombosis, number of catheter days, catheter locations, times of detection of thrombosis using Doppler ultrasonography, treatment methods and durations, thrombosis follow-up and examinations were obtained retrospectively from the electronic patient files.

Results: Ninety-six patients whose complete data could be reached were enrolled in the study. The mean gestational age of the patients was found as 29±2 weeks and the mean birth weight was 1353±369 g. Portal vein thrombosis was detected in 13.5% (n=13) of the patients. Five of the cases of portal vein thrombose were complete occlusion and eight were partial occlusion. All patients with complete occlusion and six patients with partial occlusion were treated with low-molecular-weight heparin

Öz

Amaç: Yenidoğan döneminde sıklıkla kullanılmakta olan göbek ven kateterlerine bağlı olarak, ultrasonografi taramalarında %1,3-43 arasında değişen oranlarda tromboz sıklığı bildirilmektedir. Bu çalışmada, yenidoğan yoğun bakım biriminde yatıp göbek ven kateteri takılan hastalarda, portal ven trombozu gelişme oranları ve risklerinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya 2016–2018 yılları arasında üçüncü basamak yoğun bakım biriminde yatan ve göbek ven kateteri yerleştirilen 32 gebelik hafta ve altındaki erken doğan bebekler alındı. Hastaların demografik verileri, tromboz açısından klinik risk etmenleri, kateter kalış gün sayıları, kateter yerleşim yerleri, Doppler ultrasonografi ile tromboz saptanma zamanları, tedavi yöntem ve süreleri, tromboz izlem ve tetkikleri geriye dönük olarak hastane bilgi sistemindeki elektronik hasta dosyalarından elde edildi.

Bulgular: Çalışmaya tüm verilerine ulaşılabilen 96 hasta alındı. Hastaların ortalama gebelik yaşları 29±2 hafta ve ortalama doğum ağırlıkları 1 353±369 gramdı. Hastaların %13,5'inde (n=13) portal ven trombozu saptandı. Portal ven trombozlarının beşi tam, sekizi kısmi tıkanma şeklindeydi. Tam tıkanma saptanan hastaların hepsine ve kısmi tromboz saptanan altı hastaya ortalama 31±13,8 gün düşük molekül ağırlıklı hepa-

Cont. ➡

Cite this article as: Çakır SÇ, Özkan H, Dorum BA, et al. The danger awaiting premature babies: Portal vein thrombosis. Turk Pediatri Ars 2020; 55(3): 257–62.

Corresponding Author/Sorumlu Yazar: Salih Çağrı Çakır E-mail/E-posta: salihcagri@gmail.com
Received/Geliş Tarihi: 06.07.2019 **Accepted/Kabul Tarihi:** 30.03.2020

DOI: 10.14744/TurkPediatriArs.2020.65289

for a mean duration of 31±13.8 days. Thrombosis disappeared in 7–120 days in all patients. A thrombophilia mutation was detected in six patients with thrombosis, four of whom had the PAI-1 4G / 5G mutation.

Conclusion: Portal vein thrombosis which has a significant place among the causes of portal hypertension in childhood, is mostly asymptomatic in the neonatal period and cannot be recognized clinically. It is important to screen and follow up patients with umbilical vein catheters using Doppler ultrasonography in terms of PVT after catheter removal to prevent long-term complications.

Keywords: Newborn, portal vein thrombosis, premature, umbilical vein catheter

rin tedavisi uygulandı, hastaların tümünde tromboz 7–120 gün arasında kayboldu. Tromboz saptanan altı hastada trombofili mutasyonu saptandı, dördü PAI-1 4G/5G mutasyonu şeklindeydi.

Çıkarımlar: Çocukluk döneminde portal hipertansiyon nedenlerinden olan portal ven trombozları yenidoğan döneminde çoğunlukla semptomsuz olup klinik olarak tanınamamaktadırlar. Göbek ven kateteri yerleştirilen hastaların kateter çekildikten sonra portal ven trombozu açısından Doppler ultrasonografiyle taranması ve izlemi, uzun dönem komplikasyonların önlenmesi için önemlidir.

Anahtar sözcükler: Erken doğan, göbek ven kateteri, portal ven trombozu, yenidoğan

Introduction

Babies admitted to neonatal intensive care units (NICU) frequently need central vascular access for total parenteral nutrition (TPN) and administration of drugs and blood products (1). In a newborn, placement of an umbilical venous catheter (UVC) is the most appropriate way for this objective (1). However, infection, thrombosis, and mechanical complications due to UVC may be observed (2). Vascular endothelium damage caused by the catheter, and disruption in blood flow because of the catheter and administration of substances such as TPN contribute to the occurrence of thrombosis (2). The most common reason for thrombosis in newborns is central catheters (2). In addition, preterm babies have a lifetime increased risk of thromboembolism (3). In autopsies, the frequency of UVC-related thrombosis has been reported as 65%, and catheter-related portal vein thrombosis (PVT) has been reported with frequencies ranging between 1.3% and 43% in different clinical studies (2, 4).

Portal vein thrombosis leads to serious complications such as hepatic atrophy and portal hypertension in the long term and can be recognized only by ultrasonographic screening because it is asymptomatic in the neonatal period (5). In the screening of PVT, ultrasonography can be frequently used as a reliable method (6).

In this study, it was aimed to determine the rates of PVT and its risks in preterm babies below 32 gestational weeks who underwent UVC insertion and were followed up in a tertiary care NICU.

Material and Methods

Patients

Preterm babies born at the 32nd gestational week and earlier who were hospitalized in a tertiary NICU and underwent UVC insertion between 2016 and 2018 were included in the study. Approval was obtained for the study from the local ethics committee (decision number: 2019-9/18, date: 28/05/2019). The study was conducted in accordance with the Helsinki Declaration. The patients' demographic data, catheter dwell times in days, number of administrations of erythrocyte suspensions by way of the catheter, duration of TPN, catheter insertion sites, times of detection of thrombosis using Doppler ultrasonography, treatment methods and durations, thrombosis follow-ups, and thrombosis investigations were retrospectively obtained from electronic patient files in the hospital information system. Subjects whose birth weights were below the 10th percentile by gestational week were considered small for gestational age (SGA). Babies who had a congenital anomaly, who were referred from another center after UVC insertion, and those who died were not included in the study.

Clinical applications

In our unit, UVCs are inserted in all babies at and below the 32nd gestational week who are hospitalized in the NICU on the first day of hospitalization and TPN is initiated. The UVC model used during the years when the study was conducted was the same in all patients (single-lumen 3.5–5 French catheter). The length of catheter placement was determined using Shukla's birth weight ([3×birth weight (Kg)+9)]/2+1) formula and subsequently confirmed by X-ray. In all these babies, a complete blood count is obtained on the first day. Inserted UVCs are immediately removed in cases where the need for a central venous catheter is eliminated. In patients in whom the need for central vascular access continues, the UVC is removed by opening a different central vascular access on the 14th day. In cases where another central vascular access is not possible, UVC can be used up to 28 days at most. Umbilical vein catheters are also used for obtaining blood sample as well as the administration of drugs and TPN. For blood transfusions, peripheral vascular access is preferred. However, blood products can also be administered by way of UVCs when peripheral vascular access is not possible. Heparin (0.5 U/mL) is added in the fluid given by UVCs.

All patients are evaluated in terms of PVT using Doppler ultrasonography after the UVC is removed. In patients in whom PVT is found, Factor II (G20210A), Factor V (G1691A, Leiden), Factor V (1299), methyltetrahydrofolate reductase (MTHFR) (C677T), MTHFR (A1298C), and plasminogen activator inhibitor Type 1 (PAI-1 4G/5G) mutations are inves-

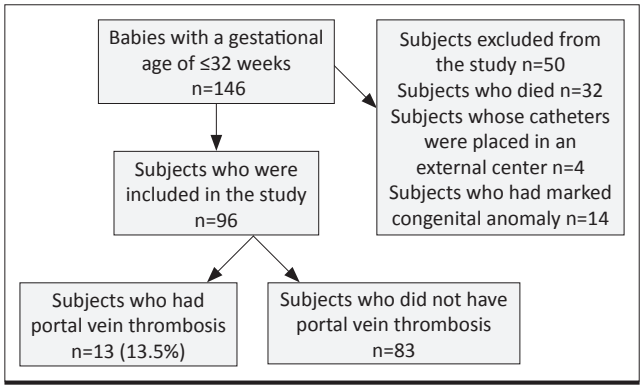

Figure 1. Patient admission flowchart

tigated in terms of the causes of thrombosis. Low-molecular-weight heparin (LMWH) treatment is initiated in cases of complete thrombosis and in cases of partial thrombosis that continue and show enlargement on the follow-up ultrasonographic examination at the 48–72nd hour.

The patients' X-rays are reevaluated to determine the placement site of UVC tip. The UVC placement sites are classified into three groups as high, hepatic, and low placement site. When the UVC tip is at the conjunction of the inferior vena cava and right ventricle and above on X-ray, it is classified as high placement site. When the catheter tip is at the level of the liver, it is classified as hepatic placement site. When the catheter tip is below the lower border of the liver, it is classified as low placement site (6).

Statistical Analysis

Analyses of the data were performed using the Statistical Package for the Social Sciences (SPSS-23). As the number of the subjects with portal vein thrombosis did not reach a number that could constitute statistically sufficient strength, descriptive tests were used without using hypothesis tests.

Results

All data of 146 patients with a gestational week of 32 and below could be reached for the study. Among these patients, 32 patients who died, four patients who underwent UVC insertion in an external center, and 14 patients who had marked congenital anomalies were excluded, and the data of 96 patients were examined. The patient admission flowchart is shown in Figure 1.

Fifty-two percent of the patients were male. The mean gestational age was 29±2 weeks and the mean birth weight was 1353±369 g. Evaluations using ultrasonography were performed after a median period of 4 (range, 2–30) days after removal of the UVC. PVT was found in 13.5% (n=13) of the patients. The demographic, clinical, and laboratory characteristics of the patients who were and were not found to have PVT are shown in Table 1. The patients' birth weights, gestational ages, 1–5 min Apgar scores, maternal preeclampsia rates, the rates of SGA and sepsis, number of days of TPN, number of administrations of erythrocyte suspensions, and hematocrit rates are shown.

Table 1. Demographic and clinical characteristics of the patients

	PVT (n=13)	No PVT (n=83)
Gestational week, mean±SD	30.2±1.4	29±2
Birth weight (g), mean±SD	1530±300	1325±372
Sex male, n (%)	7 (54)	43 (52)
Apgar 1st minute, mean±SD	6.6±1.3	5.8±2
Apgar 5th minute, mean±SD	8.2±0.6	7.7±1.5
Small for gestational age, n (%)	0 (0)	6 (0.7)
Preeclampsia, n (%)	2 (15)	13 (15.6)
Sepsis, n (%)	3 (23)	22 (26.5)
Total parenteral nutrition days, mean±SD	10.1±4.1	12.2±4.2
Number of erythrocyte transfusions, mean±SD	0.76±0.36	0.79±0.11
Hematocrit g/dL, mean±SD	46±8	48±5

PVT: Portal vein thrombosis; SD: Standard deviation

Table 2. Catheter dwell times and rates of catheter location sites

	PVT (n=13)	No PVT (n=83)
Catheter dwell time (days), mean±SD (min.–max.)	10.5±4.3 (6–21)	12.2±4.1 (2–21)
Catheter location, n (%)		
High	6 (46)	24 (29)
Hepatic	6 (46)	54 (65)
Low	1 (8)	5 (6)

PVT: Portal vein thrombosis; SD: Standard deviation; Min.: Minimum; Max.: Maximum

The catheter use durations and catheter placement sites in the patients who did and did not develop PVT are shown in Table 2. Complete thrombosis was present in five of the patients who developed PVT and partial thrombosis was present in eight. LMWH treatment was administered in all patients who were found to have a complete obstruction and in six of the patients who were found to have a partial obstruction. PVT disappeared in a median period of 22 (range, 7–220) days in all patients.

Table 3. Results of thrombophilia mutation analyses and the types of thrombosis in patients with portal vein thrombosis

Mutations studied	Type of mutation, number of patients with mutation and the degree of thrombosi			
Mutation type	Heterozygous		Homozygous	
Degree of thrombosis	Complete obstruction	Partial obstruction	Complete obstruction	Partial obstruction
Factor II (G20210A)	–	–	–	–
Factor V (G1691A, Leiden)	–	–	–	–
Factor V (1299)	1	–	–	–
MTHFR (C677T)	–	–	1	–
MTHFR (A1298C)	–	–	–	–
PAI-1 4G/5G	1	2		1

MTHFR: Methylenetetrahydrofolate reductase; PAI-1: Plasminogen activator inhibitor Type 1

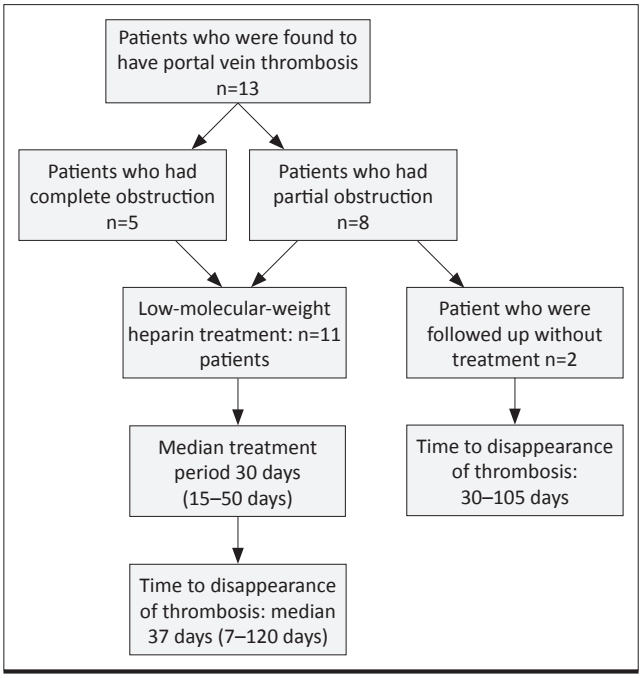

Figure 2. Summary of follow-up and treatment management in patients with portal vein thrombosis

The median LMWH treatment was 30 (range, 15–50) days, and thrombosis disappeared in a median period of 30–305 days. The treatment and follow-up management of the patients with PVT is summarized in Figure 2.

A thrombophilia mutation was found in six patients with thrombosis and four of these were PAI-1 4G/5G mutation. The mutations that were studied and were found to be significant are shown in Table 3 in association with the degrees of thrombosis.

Discussion

Frequency

The incidence of PVT related to UVC inserted in the neonatal period shows differences according to the imaging method used in studies and by timing (between 1.3% and 43%) (7). PVT rates may be found to be low due to the time of ultrasonographic examination delays or because of patients whose thromboses have spontaneously disappeared (7). In the literature, low gestational week has been reported to be a risk factor in terms of thrombosis; the babies in our study had a gestational age of 32 weeks and below and the rate of PVT in this risky group was found as 13.5% (2). In studies in which the incidence of PVT was found to be much higher, screening with ultrasonography performed while the catheter was in place, in contrast to our study (6). In our study, ultrasonographic examinations were performed 2–30 days after the UVC was removed (median: on the fourth day). It was not possible to determine on which day thrombosis developed because all portal Doppler ultrasound examinations were performed after the catheter was removed. In this regard, prospective studies involving monitoring with Doppler ultrasound imaging throughout the catheter dwell time should be conducted.

Risk factors

Kim et al. (6) found a catheter dwell time longer than 6 days to be a risk factor for the development of thrombosis. However, no significant difference was found between short-term (7–10 days) and long-term (up to 28 days) dwell times in terms of the development of infection and thrombosis (8). In a study in which UVC dwell times were very short (3.4±1.94 vs. 3.5±2.03 days), no correlation was found between catheter dwell time and the development of PVT (7). Because the patients in our study were preterm babies who needed central vascular access for longer than 6 days, the median UVC dwell times were found to be 10 (range, 6–21) days and 12 (range, 2–21) days in patients who did and did not develop PVT, respectively.

The American National Center for Disease Control and Prevention Committee recommends that UVCs should be removed in the shortest time possible and catheter dwell

time should be limited to 14 days, if possible (9). However, it was reported that randomized controlled studies were required to clearly determine the effects of catheter dwell times on the rates of disability and mortality in the 2017 Cochrane meta-analysis in which the effects of UVC dwell times were examined (10).

In a study that investigated the effect of catheter placement site on the development of PVT, the highest risk was found in hepatic placement site and the lowest risk was found in low placement site (6). However, no statistically significant difference was found between the placement sites in terms of the development of PVT (6). In our study, both groups of placement sites were similar to the literature.

In the literature, SGA, maternal preeclampsia, sepsis, asphyxia, a hematocrit value of >55%, long-term TPN, and transfusion of blood products have been defined to be risk factors in terms of the development of thrombosis (2). In our study, the presence of these risk factors was identified in both patients who did and did not develop thrombosis.

Follow-up and treatment

The efficacy of heparin as a prophylactic treatment for the prevention of the development of thrombosis could not be demonstrated (11). The efficacy of continuous heparin infusion (0.5 U/kg/h) in preventing the occurrence of thrombosis could not be demonstrated, though it decreased catheter obstruction and increased the usage time of catheters (1).

The rates of disappearance for UVC-related nonobstructive thrombi (70–77%) are higher compared with obstructive thrombi (31–48%), and it has been reported that asymptomatic thrombi can be followed up without treatment (1). However, treatment with LMWH is recommended for symptomatic or progressive thrombi (1). Treatment should be continued for six weeks to three months (1). The mean resolution time for portal vein thrombosis is 63 (range, 2–626) days and a 5-year follow-up is recommended in terms of portal hypertension (1). In our patients, the median resolution time for thrombosis was found as 37 (range, 7–120) days.

Genetics of thrombosis

It is thought that most catheter-related neonatal cases of thrombosis are associated with acquired causes and routine thrombophilia mutation study is not recommended (12). In a small number of studies that examined the genetic factors causing a predisposition to thrombophilia in patients with portal vein thrombosis, different results were reported (5). Although a significant correlation was not found between Factor V Leiden and MTHFR mutation and the risk of UVC-related thrombosis in one study, significantly higher rates of Factor V 1691 GA, MTHFR mutations, and increased homocysteine levels were found in subjects who developed PVT in another study (5). In our study, a mutation was found in a total of six patients, including three patients with partial obstruction and three patients with complete obstruction. A heterozygous Factor V (1299) mutation was found in one patient, a homozygous MTHFR (C677T) mutation was found in one patient, and a PAI-1 4G/5G mutation was found in four patients, including a homozygous mutation in one patient and heterozygous mutation in three patients. However, a comparison could not be made because there was no control group in which thrombophilia genetics was studied.

Long-term follow-up results

PVTs in the neonatal period may cause portal hypertension and gastrointestinal hemorrhage in childhood (4). It has been reported that hepatic left lobe atrophy develops at the age of 2–8 years in 25% of patients who develop PVT in the neonatal period, splenomegaly develops in 7%, and pulmonary hypertension requiring porta-caval shunt surgery develops in 3% (13). In addition, it has been observed that there is a history of umbilical vein insertion in the neonatal period in 37% of cases of extrahepatic portal vein obstruction, which is found in childhood and is the most important cause of portal hypertension (14). It is important to screen patients with UVC using Doppler ultrasonography in terms of PVT and to treat and follow up those who are found to have PVT, especially to prevent long-term negative outcomes. Some patients who have PVT are followed up with ultrasonographic examination without treatment. However, study results show that a significant portion of patients who are followed up as outpatients (22.5%) do not attend their follow-up visits (4). The fact many patients are being followed up as outpatients without treatment do not attend their follow-up visits increases the risk of negative outcomes.

The days of Doppler ultrasonography and the experts performing ultrasonographic examinations could not be standardized because the study was retrospective. Also, thrombophilia genetics were studied only in patients who developed thrombosis; a comparison could not be made because the patients who did not have thrombosis were not evaluated in this aspect. The number of subjects examined remained limited because the patient group who underwent the same clinical applications in a certain period were examined in this retrospective study and statistical hypothesis tests could not be performed.

In conclusion, PVT, which has a significant place among the causes of portal hypertension in childhood, is mostly asymptomatic in the neonatal period and cannot be recognized clinically. It is important to screen and follow up patients with UVCs using Doppler ultrasonography in terms of PVT after catheter removal to prevent long-term complications. Multi-center prospective studies involving higher numbers of patients are needed for better epidemiologic information and statistical data analysis in terms of portal vein thrombosis.

Ethics Committee Approval: Approval was obtained from the local ethics committee with decision number 2019-9/18 dated 28/05/2019 for the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.K., H.Ö., S.Ç.Ç., B.B., A.M.G., M.S.E., P.K., B.A.D; Design - N.K., H.Ö., S.Ç.Ç., B.B., A.M.G., M.S.E., P.K., B.A.D.; Supervision - N.K., H.Ö., S.Ç.Ç., B.B., A.M.G., M.S.E., P.K., B.A.D.; Data Collection and/or Processing - N.K., H.Ö., S.Ç.Ç., B.B., A.M.G., M.S.E., P.K., B.A.D.; Analysis and/or Interpretation - N.K., H.Ö., S.Ç.Ç., B.B., A.M.G., M.S.E., P.K., B.A.D.; Literature Review - N.K., H.Ö., S.Ç.Ç., M.S.E.; Writing - N.K., H.Ö., S.Ç.Ç., B.B., M.S.E., B.A.D.; Critical Review - N.K., H.Ö., S.Ç.Ç., B.B., M.S.E., B.A.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Kurul Onayı: Çalışma için bölgesel etik kurul komitesinden 28/05/2019 tarih ve 2019-9/18 karar numarası ile onay alındı.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - N.K., H.Ö., S.Ç.Ç., B.B., A.M.G., M.S.E., P.K., B.A.D.; Tasarım - N.K., H.Ö., S.Ç.Ç., B.B., A.M.G., M.S.E., P.K., B.A.D.; Denetleme - N.K., H.Ö., S.Ç.Ç., B.B., A.M.G., M.S.E., P.K., B.A.D.; Veri Toplanması ve/veya İşlemesi - N.K., H.Ö., S.Ç.Ç., B.B., A.M.G., M.S.E., P.K., B.A.D.; Analiz ve/veya Yorum - N.K., H.Ö., S.Ç.Ç., B.B., A.M.G., M.S.E., P.K., B.A.D.; Literatür Taraması - N.K., H.Ö., S.Ç.Ç., M.S.E.; Yazıyı Yazan - N.K., H.Ö., S.Ç.Ç., B.B., M.S.E., B.A.D.; Eleştirel İnceleme - N.K., H.Ö., S.Ç.Ç., B.B., M.S.E., B.A.D.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

References

1. Park CK, Paes BA, Nagel K, Chan AK, Murthy P; Thrombosis and Hemostasis in Newborns (THiN) Group. Neonatal central venous catheter thrombosis: diagnosis, management and outcome. Blood Coagul Fibrinolysis 2014; 25: 97–106.
2. Revel-Vilk S, Ergaz Z. Diagnosis and management of central-line-associated thrombosis in newborns and infants. Semin Fetal Neonatal Med 2011; 16: 340–4.
3. Zöller B, Li X, Sundquist J, Sundquist K, Crump C. Gestational age and risk of venous thromboembolism from birth through young adulthood. Pediatrics 2014; 134: e473–80.
4. Morag I, Epelman M, Daneman A, et al. Portal vein thrombosis in the neonate: risk factors, course, and outcome. J Pediatr 2006; 148: 735–9.
5. Bhatt MD, Patel V, Butt ML, Chan AKC, Paes B; Thrombosis and Hemostasis in Newborns (THiN) Group. Outcomes following neonatal portal vein thrombosis: A descriptive, single-center study and review of anticoagulant therapy. Pediatr Blood Cancer 2019; 66: e27572.
6. Kim JH, Lee YS, Kim SH, Lee SK, Lim MK, Kim HS. Does umbilical vein catheterization lead to portal venous thrombosis? Prospective US evaluation in 100 neonates. Radiology 2001; 219: 645–50.
7. Gharehbaghi MM, Nemati M, Hosseinpour SS, Taei R, Ghargharechi R. Umbilical vascular catheter associated portal vein thrombosis detected by ultrasound. Indian J Pediatr 2011; 78: 161–4.
8. Butler-O'Hara M, Buzzard CJ, Reubens L, McDermott MP, DiGrazio W, D'Angio CT. A randomized trial comparing long-term and short-term use of umbilical venous catheters in premature infants with birth weights of less than 1251 grams. Pediatrics 2006; 118: e25–35.
9. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis 2011; 52: e162–93.
10. Gordon A, Greenhalgh M, McGuire W. Early planned removal of umbilical venous catheters to prevent infection in newborn infants. Cochrane Database Syst Rev 2017; 10: CD012142.
11. Unal S, Ekici F, Cetin İİ, Bilgin L. Heparin infusion to prevent umbilical venous catheter related thrombosis in neonates. Thromb Res 2012; 130: 725–8.
12. Celkan T, Dikme G. Thrombosis in children: Which test to whom, when and how much necessary? Turk Pediatri Ars 2018; 53: 1–9.
13. Morag I, Shah PS, Epelman M, Daneman A, Strauss T, Moore AM. Childhood outcomes of neonates diagnosed with portal vein thrombosis. J Paediatr Child Health 2011; 47: 356–60.
14. Alvarez F, Bernard O, Brunelle F, Hadchouel P, Odièvre M, Alagille D. Portal obstruction in children. I. Clinical investigation and hemorrhage risk. J Pediatr 1983; 103: 696–702.