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Complete List of Authors:	van Rens, Matheus F.P.T.; Hamad Medical Corporation Hugill, Kevin; Hamad Medical Corporation Mahmah, Mohamad A.; Hamad Medical Corporation Bayoumi, Mohammad A.A.; Hamad Medical Corporation Francia, Airene L.V.; Hamad Medical Corporation Garcia, Krisha L.P.; Hamad Medical Corporation Loon, Fredericus HJ; Fontys University of Applied Sciences, Department of Science and Technology in Anesthesia Nursing; Catharina Hospital, Department of Science and Technology in Anesthesia Nursing
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Evaluation of unmodifiable and potentially modifiable factors affecting peripheral intravenous device related complications in neonates: a retrospective observational study.

Matheus F.P.T. van Rens[1], Kevin Hugill[1], Mohamad A. Mahmah[1], Mohammad A.A. Bayoumi[1], Airene L.V. Francia[1], Krisha L.P. Garcia[1], Fredericus H.J. van Loon[2,3].

Affiliations: [1] Neonatal Intensive Care Unit, Women's Wellness and Research Center, Hamad Medical Corporation, Doha, Qatar; [2] Department of Science and Technology in Anesthesia Nursing, Fontys University of Applied Sciences, Eindhoven, The Netherlands; and [3] Department of Anesthesiology, Catharina Hospital, Eindhoven, The Netherlands.

Address correspondence to: F.H.J. van Loon. Post to: Fontys University of Applied Sciences, Department of Technical and Anesthesia Nursing Sciences, Ds. Th. Fliednerstraat 2, Building TF, 5631 BN Eindhoven, The Netherlands. Email to: rick.vanloon@fontys.nl.

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ABSTRACT

Objectives: Infants in neonatal units benefit from dependable peripheral intravenous access. However, peripheral intravenous access exposes infants to high rates of clinically minor and serious complications, despite this little is known about the interplay of risk factors. The aim of this study was to assess the incidence and evaluate the interactions of risk factors on the occurrence of peripheral intravenous complications in a neonatal population. **Design:** This was a retrospective observational study. **Setting:** The study was performed on the NICU. **Participants:** This study included 12978 neonates who required intravenous therapy. **Outcome measurements:** The main outcome was the occurrence of any complication in relation to PIVC use, leading to unplanned removal of the device before completion of the intended intravenous therapy. **Results:** A mean dwell time of 36±28 hours was recorded in participants with no complications, whereas the mean dwell time was 31±243 hours in participants with an indication for premature removal of the PIVC (P<0.001, t=11.35). Unplanned removal occurred in 59% of cases, the overall complication rate was 18 per 1000 catheter days. Unmodifiable factors affecting PIVC dwell time include lower birth (P<0.001, t=5.49) and current body weight (P<0.001, t=5.51). Cannulation site (P<0.001, χ^2=69.00, df=6), the inserted device (P<0.001, χ^2=99.51, df=3) and the indication for IV treatment (P<0.001, χ^2=409.12, df=4) were modifiable factors. **Conclusions:** Most infants experienced a vascular access related complication. Given

the high complication rate, PIVC should be used judiciously and thought given prior to their use as to whether alternate means of IV access might be more appropriate.

Strengths and limitations of this study

- This was an observational study including a large sample of 12978 neonates.
- This study provide information on the risk of complications regarding peripheral intravenous cannulation in neonates.
- This study is based on a retrospective analyses of collected data.

INTRODUCTION

Providing reliable vascular access in the neonatal intensive care unit (NICU) is essential to administer nutrition, fluids, medication, and blood products.[1] Critically ill and preterm infants benefit from early intravenous therapy.[2] Currently the main intravenous (IV) vascular access routes, are via peripheral and central veins. Peripheral intravenous cannulation is the most frequently performed procedure in NICU.[1,3] Preterm and ill infants are at an increased risk of peripheral intravenous catheter (PIVC) related complications.[1,3-6] In part, this is due to immature skin anatomy and physiology, immature immune system and smaller fragile blood vessels.[3-6]

PIVC related complications are a major clinical concern in NICUs. Frequently encountered complications are infiltration and extravasation (PIVIE), leakage, occlusion, thrombosis, phlebitis, infection, and dislodgment or accidental removal.[1,4,7-11] According to Pettit[12], the incidence of complications has remained constant over recent decades irrespective of clinical innovations and changes in practice. Overall, the risk for a PIVC related complication in this patient population is reported as up to 75%.[1,5,6,8,11,13] Of particular concern is the risk of PIVIE which according to several sources is high in the neonatal population, having an incidence of around 65%.[1,4,8,12] Infection rates are highly variable, but have been documented as between 2 to 49 incidents per 1000 catheter days.[14]

Extrinsic modifiable factors influence PIVC dwell time, such as clinician training, exposure, experience, choice of the optimal PIVC for the right patient for the right therapy, site selection and preparation, insertion technology, maintenance care bundles, stabilization materials and dressings.[3-5,15] Recent evidence from large scale studies in neonatal populations regarding factors influencing PIVC is lacking and absent for Middle Eastern settings and contexts. The current study aims to identify and evaluate the relationships between unmodifiable and potentially modifiable factors with the presence of PIVC related complications.

METHODS

Design and setting

This retrospective observational study uses routinely collected anonymized data from January 2019 to July 2020. The outcome of interest was the occurrence of any complication in relation to PIVC use, leading to unplanned removal of the device before completion of the intended intravenous therapy. The study was carried out on the NICU (112 cots) of the Women's Wellness and Research Centre (WWRC) of Hamad Medical Corporation (HMC), Doha, Qatar. The study protocol (MRC-01-20-594) was approved by the local institution review body (IRB). As the data source was anonymized, the local IRB deemed that participant consent was not feasible nor required as they determined the study a 'chart review'. Participants and their parents were not involved in the design, conduct or reporting of this study.

Participants and sample size

Infants who were admitted to the NICU and who required intravenous therapy were included in this study. Participants were excluded from the sample if the data collection was incomplete or related to the use of other devices (centrally inserted central catheters or peripherally inserted central catheters).

Procedure

Peripheral intravenous cannulation was performed according to hospital policy based on international guidelines.[16] In the study setting peripheral intravenous cannulation is routinely performed by nurses from the NICU vascular access team (VAT). The selection of suitable veins was done using the VeinViewer® (Christie Medical Holdings Inc., Lake Mary, FL, USA) with the saphenous and elbow veins generally avoided. Vein length, valves, and potential for the vein to fill and empty itself were prior assessed using a standardized approach to appraisal of the potential site. Short peripheral intravenous catheters were used if therapy was predicted for up to two days, including a 26 or 24-gauge Neoflon™ Pro (Becton Dickinson Infusion Therapy, Sandy, UT, USA) or a 26-gauge SuperCath™ Safety (ICU Medical, San Clemente, CA, USA). Extended 22-gauge peripheral intravenous catheters were inserted when duration of therapy was expected to last for 5 days (LeaderFlex, Vygon, Lansdale, PA, USA). In situations where intravenous therapy was expected to last more than 5 days central venous access is preferred.

Measurements and data collection

Patients demographics and baseline data included sex, gestational age at birth in weeks and days, birth weight, and current body weight in grams. Data regarding the procedure of peripheral intravenous cannulation were the date and time of cannulation, as well as the number of attempts needed to successful cannulation, cannulation side (left or right), extremity of cannulation and the site on the extremity (dorsum of the hand, wrist and lower arm, elbow crease and upper arm, foot, ankle and lower leg, or

knee and upper leg), size of device (22, 24, or 26 gauge), the indication for intravenous treatment (intravenous fluids, medications, total parenteral nutrition, blood and blood products, blood extraction, or procedural), the date and time of removal of the PIVC, total dwell time of the PIVC in hours (calculated as the removal date and time minus the insertion date and time), and the reason for removal of the PIVC (therapy completed and elective removal, PIVIE, phlebitis, occlusion, dislodgement and accidental removal, discoloration, patient transferred or expired). Furthermore, additional data points included the use of catheter securement glue, application of ivWatch® (ivWatch LLC., Newport News, VA, USA), if the touch-look-compare observation tool was used, and calculation of the PIVIE Severity Score in percentages.[17,18] The ivWatch® was introduced into use in January 2020 and applied since then with infants weighing more than 1000 grams.

Statistical analyses

Descriptive statistics were used to summarize the outcomes with a mean and its standard deviation or median and its range for continuous variables regarding its normal distribution, and absolute numbers with percentage for discrete variables. The assumption of normal distribution was proved with Kolmogorov-Smirnof testing. Differences regarding outcomes and measurements were demonstrated by using the χ^2-test, Mann-Whitney *U* test, or unpaired samples *t* test, as appropriate. Stepwise multivariate logistic regression analyses were used to provide correlations between variables regarding the outcome of interest and obtain its odds ratio with 95%

confidence interval. Items with a significant relationship ($P<0.01$) to the outcome of interest from a univariate logistic regression technique were entered in these analyses. The stepwise method was utilized to remove independent variables that did not make a significant contribution to the primary outcome variable using a backward elimination process based on the Wald statistic and level of significance, with the removal criteria set at $P=0.01$, to obtain a model with a minimal set of variables and a maximal correlation coefficient (Nagelkerke R^2). Correlation between variables was measured by determining Pearson's or Spearman's ρ, as appropriate. Survival analyses of the PIVC in terms of its dwell time were performed by plotting a Kaplan-Meier curve. Differences between survival time of the PIVC according to its reason for premature removal were represented with Mantel-Cox χ^2. A $P<0.05$ was denoted to be statistically significant throughout this study. SPSS (version 25.0; SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

RESULTS

In total, data on 15087 cannulation events in neonates was collected during the study period, of which data of 2109 participants were removed due to incompleteness, including failure to insert. The final database included 12978 participants, with 7695 (59%) being of male sex. Mean duration of gestation was 34+6 weeks. Current age in days after birth was 9 (0 to 29) days at the time that peripheral intravenous cannulation was performed. Mean weight at birth was 2334±975 grams, with a mean current weight of 2410±931 grams at the time of cannulation.

Successful peripheral intravenous cannulation at the first attempt was obtained in 8481 participants (65%). 24% needed two attempts, 8%, 2% needed three attempts and a small number, under senior clinician oversight needed more attempts to successfully insert a PIVC. Throughout the study were 19329 insertion attempts performed to create peripheral intravenous access. Data regarding the procedure of peripheral intravenous cannulation is summarized in Table 1.

Failure of the PIVC, resulting in premature removal, occurred in 7627 participants (59%). In 5145 participants (40%), the PIVC was removed after completion of intravenous therapy. In 142 cases (1%) was the participant transferred or expired (administrative censoring). A mean dwell time of 36±28 hours was recorded in participants with no complications, whereas the mean dwell time was 31±243 hours in participants with an indication for premature removal of the PIVC (P<0.001, t=11.350).

Subsequently, there was a correlation between dwell times and the occurrence of a PIVC related complication (P<0.001, ρ=-0.099). The overall PIVC complication rate was 18 per 1000 catheter days. Additional information according to the reason for removal of the PIVC is shown in Table 2.

Total dwell time of the device in each participant until its moment of removal is represented in Figure 1. 50% of PIVC were removed within the first 38 hours. Dwell times differed regarding the reason for removal or the kind of PIVC related complication (P<0.001, χ^2=76.834, df=4).

As shown in Table 3, twelve variables had a significant relation with the outcome of interest in the univariate logistic analyses, resulting in premature removal of the device. These items were used for multivariate analyses, resulting in a smallest set of five variables correlating with the outcome of interest (R^2=60%) (Table 4).

A lower weight at birth (P<0.001, t=5.486) and a lower current body weight (P<0.001, t=5.508) resulted in an increased risk for PIVC related complications. Cannulation on the hand showed the lowest complication rate (57%), whereas most complications were reported after cannulation on the ankle or lower leg (72%) (P<0.001, χ^2=69.001, df=6). Inserting a 22-gauged device resulted in 77% of cases in a complication, cannulation with a 26-gauged catheter lead to complications in 49% of insertions (P<0.001, χ^2=99.513, df=3). If TPN was the indication for starting up intravenous treatment, 64% resulted in premature removal of the device, whereas only 18% of insertion resulted in a complication if cannulation was performed per procedure and elective (P<0.001, χ^2=409.120, df=4).

The PIVIE Severity Score was higher in participants with an indication for premature removal of the device (13.1±8.6) when compared to those without a VAD related complication (0.8±4.1) (P<0.001, t=-25.409). PIVIE Severity Scores were in increased in participants suffering from PIVIE (13.8±8.0) and phlebitis (12.9±9.9). Furthermore, a correlation between the PIVIE Severity Score and device dwell time could be obtained (P<0.001, ρ=-0.122). The ivWatch® was applied in 12% of participants, of which 63% suffered from premature removal. The added value of this device resulted in a sensitivity of 57% and a specificity of 56% (P<0.001, χ^2=54.165, df=1). Catheter dwell times of 33±22 were seen after the application of ivWatch®, which did not differ from dwell times of 33±25 in participants in whom the technique was not used (P=0.705, t=-0.379). Moreover, a correlation between the application of the ivWatch® and device dwell times could not be obtained (P=0.705, ρ=-0.006). The touch-look-compare observation tool was applied in 67% of cases and detected complications in 61% of participants with an event (P=0.002, χ^2=9.975, df=1). The use of the touch-look-compare observation tool resulted in a sensitivity of 97% and a specificity of 96% and correlated with device dwell time (P=0.001, ρ=-0.032). The use of glue for fixation of the PIVC increased the dwell time to 34±25 when compared to participants in which no glue was used (dwell time of 28±18), although the difference was not significant (P=0.057, t=-1.902). A correlation could not be seen between the use of glue and PIVC dwell times (P=0.025, ρ=-0.106).

DISCUSSION

The incidence of VAD failure is high in clinical practice, which negatively affects a neonate's comfort and outcome.[19-21] Failure of peripheral inserted PIVC, resulting in premature removal, occurred in 51% of participants, with a complication rate of 18 per 1000 device days. The most frequently reported complications were PIVIE and phlebitis. The risk for complications was increased in participants with a lower weight at birth and current body weight. Furthermore, the cannulation site, size and type of device, and the indication for intravenous treatment affected the risk for failure as well.

Although this study provide information on the risk of complications regarding peripheral intravenous cannulation in neonates, majority of it was reported in many articles. Nonetheless, to the best of our knowledge, a study including as many patients as the current study does was never published before on this topic.

Peripheral intravenous catheters are often the primary and most commonly inserted devices used to obtain vascular access during hospitalization.[19] The incidence of device failure in the current study is slightly higher when compared to the 34% pooled incidence of failure in the recently published meta-analyses by Indarwati et al.[21] It is difficult to give an unambiguous clarification for this, although the pattern of complications and their relative incidence does match.

PIVIE was the most common complication in infants admitted to the NICU, with an incidence of 34% in the current study. PIVIE is defined as an unintended infusion of

fluids and/or medication in the surrounding tissue, in which infiltration is the infusion of non-vesicant fluids or medication and extravasation infusion of vesicants into surrounding tissues.[5] The determination of PIVIE can be subjective, making it hard to compare the results of different studies. However, standardized training of a dedicated VAT and routine review of scores can improve consensus and reduce subjectivity. The incidence of infiltration reported elsewhere ranges from 6% to 87%, and the incidence of extravasation between 2% and 77%.[21] The use of the infiltration/extravasation staging instrument, as developed by Montgomery et al., could accomplish consensus on the definition of the condition and its severity.[5,22] An explanation for the non-standard use of this instrument may be that it has not been externally validated.

Phlebitis (inflammation of the venous wall) can cause discomfort and tissue damage. The incidence was 10% in the current study which is broadly in accord with other reports.[21,22-26] According to Arias-Fernandez et al., assessment of phlebitis is difficult because the consensus for the diagnosis is low.[27] Furthermore, a lack of consensus on phlebitis measures has likely contributed to disparities in reported phlebitis incidence.[28]

Several tools are used in clinical practice to reduce the risk or severity for premature failure of PIVCs due to device related complications. The touch-look-compare observation tool was developed at Cincinnati Children's Hospital Medical Center to reduce peripheral intravenous infiltration and extravasation injuries.[17] This documented methodical hourly assessment of patients with a PIVC can help practitioners' standardize their practice and reduce variations in quality of care.[17] Our

study showed highly discriminative effects of the touch-look-compare observation tool based on high sensitivity and specificity, which was denoted as the most decisive tool in detecting device related complications in earlier. Routine observations by combining the touch-look-compare observation tool and the PIVIE Severity Scoring instrument seems to result in the most optimal situation regarding the early detection of complications.

It is known that the preferred cannulation site is the dorsal hand, on which fewer attempts were required for successful cannulation, with fewer complications and extended dwell times.[13] This is in accordance with the results of the current study. Moreover, phlebitis caused by mechanical irritation due to the device is thought to be an important factor for failure.[20] Fixation of the device after insertion with glue increases the stability of the device. Despite no significance could be obtained, dwell times were increased after using glue in this study. Highest incidence of premature removal of the device was seen with a 22-gauged device. Insertion of a 26-gauged catheter resulted in the lowest incidence of complications. Notwithstanding, most participants in this study received a 26-gauged device, possibly leading to a distorting result. To minimize the risk for phlebitis, the smallest gauged catheter possible should be inserted and the use of extension tubes as an accessory to the device should be avoided.[26]

Preterm infants are extra sensitive to the development of PIVIE and phlebitis due to their immature immune systems.[21,29] Beall et al. concluded that the inadequate anti-inflammatory response may fail to release free radical scavengers leading to endothelial apoptosis and injury of cell membranes and vessels.[29] To add to this, it is

thought that medications or fluids with a higher osmolality increases the risk for extravasation by irritating the endothelial lining of the vein.[21] Early detection of signs and symptoms correlating positively with PIVC complications is crucial in limiting the risk for failure of the device. Assessing pain accurately in preverbal infants is challenging.[30] Moreover, additional occlusive fixtures and bandages to secure the device add limits to identifying early stages of complications, and thus timely cessation of therapy and treatment to minimize harm.[21,30] The incidence of complications could likely be reduced with consistent and quality insertion and maintenance practices. The Infusion Nurses Society provides specific recommendations for newborn infants offering further specific guidelines for insertion and management practice.[16]

Limitations

The current study was based on a retrospective collected dataset. In contrast to randomized studies, the method creates a risk for selection bias. In the present study every infant with a PIVC was included in order to minimize the risk of selection bias. In addition, this current study was carried out according to the STROBE statement.[31] Inter-rater variability might have affected the results, however, our use of standardized education and training and limiting vascular access to a small team (the VAT) will mitigate this variability in the data. Nonetheless, future research should focus on the development and validation of decisive tools and their integration with emerging technologies to identify complications early.

CONCLUSION AND RELEVANT IMPLICATIONS

Five variables were identified as factors affecting PIVC dwell time in patients admitted to the NICU. These factors include a lower weight at birth and current body weight, the cannulation site, size and type of device and the indication for intravenous treatment affected the risk for failure as well. The PIVC complication rate was 18 per 1000 catheter days in the current study. The risk for the development of a PIVC related complication, leading to premature removal of the device, increased with extended dwell times. It seems that when a PIVC is inserted it is not the question of if the infant will have a complication, but only a matter of when. Consequently, we argue that PIVC should be used judiciously and thought given prior to their use as to whether alternate means of IV access might be more appropriate.

ADDITIONAL INFORMATION

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designed the data collection instruments, collected data, and reviewed and revised the manuscript. Krisha L.P. Garcia designed the data collection instruments, collected data, and reviewed and revised the manuscript. Fredericus H.J. van Loon conceptualized and designed the study, carried out the initial analyses, and critically reviewed the manuscript for important intellectual content and revised the manuscript.

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Table 1: Procedural peripheral intravenous cannulation data

Factor	Description	Total cohort *N = 12978*	Successful first attempt *N = 8481*	Unsuccessful first attempt *N = 4497*	*P*-value
Side of cannulation	*Left*	7120 (55%)	4794 (57%)	2326 (52%)	<0.001
	Right	5854 (45%)	3684 (43%)	2170 (48%)	
Site of cannulation on the selected extremity	*Hand*	10512 (81%)	7078 (83%)	3434 (76%)	<0.001
	Wrist/ lower arm	459 (4%)	240 (3%)	219 (5%)	
	Elbow/ upper arm	61 (<1%)	33 (1%)	28 (1%)	
	Foot	1774 (14%)	1025 (12%)	749 (17%)	
	Ankle/ lower leg	119 (1%)	78 (1%)	41 (1%)	
	Knee/ upper leg	50 (<1%)	25 (<1%)	25 (<1%)	
	Scalp	2 (<1%)	1 (<1%)	1 (<1%)	
Size of the inserted catheter	*26 gauge*	12403 (96%)	8090 (96%)	4313 (96%)	<0.001
	24 gauge	141 (1%)	97 (1%)	44 (1%)	
	22 gauge	434 (3%)	294 (3%)	140 (3%)	
Indication for intravenous treatment	*IV fluids/ medications*	7283 (56%)	4781 (56%)	2502 (56%)	<0.001
	IV fluids/ TPN	4330 (33%)	2844 (34%)	1486 (33%)	
	Blood and blood products	482 (4%)	285 (3%)	197 (4%)	
	Blood extraction	708 (5%)	455 (5%)	253 (6%)	

Procedure	175 (2%)	116 (2%)	59 (1%)

Data is represented as absolute number and percentages, which were calculated as a proportion within in the cell. IV = intravenous, TPN = total parenteral nutrition.

Table 2: Data representing the reason for removal of the peripheral intravenous catheter.

Factor	Description	Device dwell time (hours)	Total cohort *N = 12914*
Reason for removal of the VAD	*Therapy completed/ elective*	37±28	5145 (40%)
	PIVIE	31±24	5159 (40%)
	Phlebitis	29±19	1590 (12%)
	Occlusion	41±29	527 (4%)
	Dislodgement/ accidental removal	23±25	286 (2%)
	Swelling or discoloration	22±20	65 (1%)
	Administrative censoring	17±26	142 (1%)

Data is represented as mean and its standard deviation or as absolute number and percentages, which were calculated as a proportion within the cell. Device dwell time is represented in hours. VAD = vascular access device, PIVIE = peripheral intravenous intravasation and extravasation. Data of 64 participants is missing.

Table 3: Univariate logistic regression analyses with factors affecting the risk for failure of peripheral intravenous access devices.

Factor	β	Odds ratio	95% confidence interval	*P* value
Sex of the participant	0.108	1.11	1.04 – 1.20	0.003
Duration of gestation in weeks	0.060	1.06	1.04 – 1.09	<0.001
Current age in days since gestation	-0.501	0.61	0.37 – 0.99	0.047
Weight at birth in grams	-0.072	0.93	0.88 – 0.97	0.002
Current weight in grams	0.037	1.04	1.01 – 1.07	0.010
Successful first attempt of intravenous cannulation	-0.026	0.97	0.91 – 1.05	0.483
Number of attempts to successful cannulation	-0.026	0.97	0.93 – 1.02	0.255
Side of cannulation	0.038	1.04	0.97 – 1.12	0.287
Site of cannulation on the extremity	0.181	1.20	1.14 – 1.26	<0.001
Size of the inserted intravenous catheter	-0.124	0.88	0.84 – 0.93	<0.001
Indication for intravenous treatment	-0.292	0.75	0.72 – 0.78	<0.001
Time of the device in situ	-0.499	0.61	0.56 – 0.65	<0.001
Application of TLC observation	0.327	1.39	1.31 – 1.70	0.002
PIVIE Severity Score	0.427	1.53	1.46 – 1.61	<0.001
Application of the ivWatch®	0.509	1.66	1.45 – 1.91	<0.001

Application of device fixation glue	0.206	1.23	0.77 – 2.00	0.383

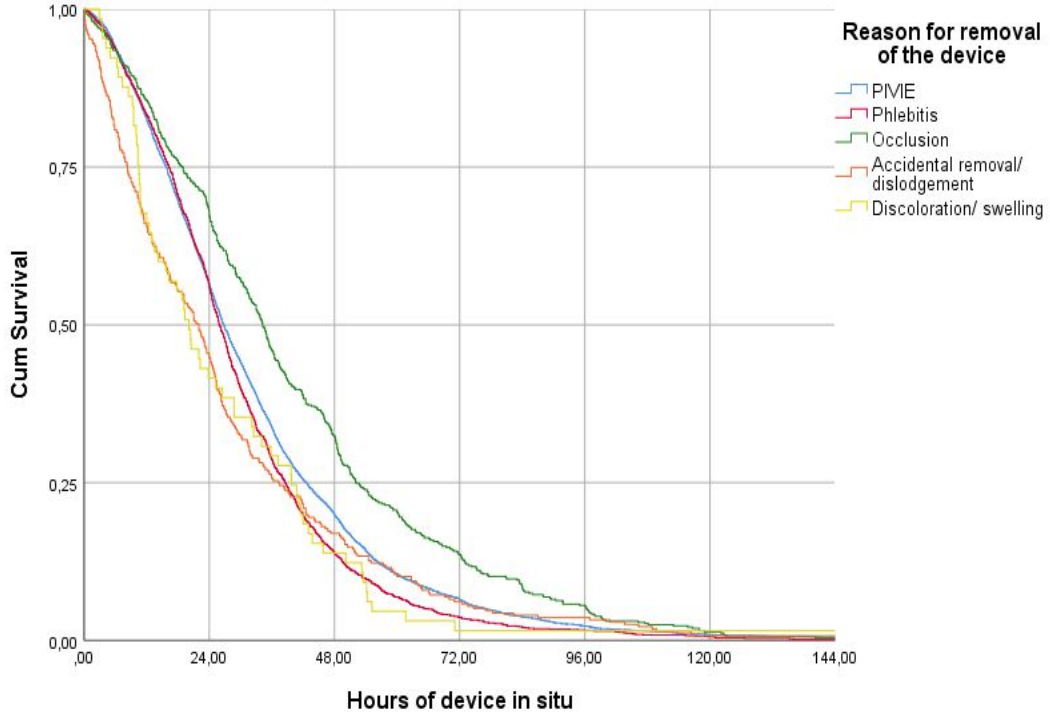
TLC = touch-look-compare*, PIVIE = peripheral intravenous infiltration and extravasation.*

Table 4: Multivariate logistic regression analyses with factors affecting the risk for failure of peripheral intravenous access devices.

Factor	β	Odds ratio	95% confidence interval	*P* value
Weight at birth in grams	-1.452	0.23	0.20 – 0.28	<0.001
Current weight in grams	0.062	1.06	1.03 – 1.10	0.001
Site of cannulation on the extremity	0.207	1.23	1.16 – 1.30	<0.001
Size of the inserted intravenous catheter	-0.119	0.89	0.84 – 0.94	<0.001
Indication for intravenous treatment	-0.280	0.76	0.73 – 0.79	<0.001

Constant β=0.518 with an odds ratio of 1.68 (P<0.001).

Figure 1: Kaplan-Meier survival analyses for peripheral intravenous catheters.



Intravenous catheters were removed after the occurrence of a complication, of which dwell times were compared between the type of complications as measured in this study. PIVIE = peripheral intravenous infiltration and extravasation.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**3**
Objectives	3	State specific objectives, including any prespecified hypotheses	**3**
Methods			
Study design	4	Present key elements of study design early in the paper	**4**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**4**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	**4**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	**4**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**5**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**5**
Bias	9	Describe any efforts to address potential sources of bias	**5**
Study size	10	Explain how the study size was arrived at	**5**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**5,6**
		(*b*) Describe any methods used to examine subgroups and interactions	**5,6**
		(*c*) Explain how missing data were addressed	**5,6**
		(*d*) If applicable, explain how loss to follow-up was addressed	**5,6**
		(*e*) Describe any sensitivity analyses	**5,6**
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**7,8**
		(b) Give reasons for non-participation at each stage	**7,8**
		(c) Consider use of a flow diagram	**7,8**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**7,8**
		(b) Indicate number of participants with missing data for each variable of interest	**7,8**
		(c) Summarise follow-up time (eg, average and total amount)	**7,8**
Outcome data	15*	Report numbers of outcome events or summary measures over time	**7,8**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**7,8**
		(*b*) Report category boundaries when continuous variables were categorized	**7,8**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**7,8**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**7,8**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**9**
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**11**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**11**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**13**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Evaluation of unmodifiable and potentially modifiable factors affecting peripheral intravenous device related complications in neonates: a retrospective observational study.

Matheus F.P.T. van Rens[1], Kevin Hugill[1], Mohamad A. Mahmah[1], Mohammad A.A. Bayoumi[1], Airene L.V. Francia[1], Krisha L.P. Garcia[1], Fredericus H.J. van Loon[2,3].

Affiliations: [1] Neonatal Intensive Care Unit, Women's Wellness and Research Center, Hamad Medical Corporation, Doha, Qatar; [2] Department of Science and Technology in Perioperative Nursing, Fontys University of Applied Sciences, Eindhoven, The Netherlands; and [3] Department of Anesthesiology, Intensive Care and Pain Medicine Catharina Hospital, Eindhoven, The Netherlands.

Address correspondence to: F.H.J. van Loon. Post to: Fontys University of Applied Sciences, Department of Technical and Anesthesia Nursing Sciences, Ds. Th. Fliednerstraat 2, Building TF, 5631 BN Eindhoven, The Netherlands. Email to: rick.vanloon@fontys.nl.

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ABSTRACT

Objectives: Infants in neonatal units benefit from dependable peripheral intravenous access. However, peripheral intravenous access exposes infants to high rates of clinically minor and serious complications. Despite this, little is known about the interplay of risk factors. The aim of this study was to assess the incidence and evaluate the interactions of risk factors on the occurrence of peripheral intravenous complications in a neonatal population. **Design:** This was a retrospective observational study. **Setting:** The study was performed on the Neonatal Intensive Care Unit (NICU) of the Women's Wellness and Research Centre, Hamad Medical Corporation, Qatar as a single site study. **Participants:** This study included 12978 neonates who required intravenous therapy. **Outcome measurements:** The main outcome was the occurrence of any peripheral intravenous cannulation failure, leading to unplanned removal of the device before completion of the intended intravenous therapy. **Results:** A mean dwell time of 36 ±28 hours was recorded in participants with no complications, whereas the mean dwell time was 31 ±23 hours in participants with an indication for premature removal of the peripheral intravenous catheter (P<0.001, t=11.35). Unplanned removal occurred in 59% of cases, the overall complication rate was 18 per 1000 catheter days. Unmodifiable factors affecting peripheral intravenous catheter dwell time include lower birth (odds ratio =0.23, 0.20 to 0.28, P<0.001) and current body weight (odds ratio =1.06, 1.03 to 1.10, P=0.018). Cannulation site (odds ratio =1.23, 1.16 to 1.30, P<0.001), the inserted device (odds ratio =0.89, 0.84 to 0.94, P<0.001) and the

indication for intravenous treatment (odds ratio =0.76, 0.73 to 0.79, $P<0.001$) were modifiable factors. **Conclusions:** Most infants experienced a vascular access related complication. Given the high complication rate, peripheral intravenous catheters should be used judiciously, and thought given prior to their use as to whether alternate means of intravenous access might be more appropriate.

Strengths and limitations of this study

- This was an observational study including a large sample of 12978 neonates.
- This study provides information on the risk of complications regarding peripheral intravenous cannulation in neonates.
- This study is based on retrospective analyses of collected data.

INTRODUCTION

Providing reliable vascular access in the neonatal intensive care unit (NICU) is essential to administer nutrition, fluids, medication, and blood products[1]. Critically ill and preterm infants benefit from early intravenous therapy[2]. Currently the main intravenous (IV) vascular access routes, are via peripheral and central veins. Peripheral intravenous cannulation is the most frequently performed procedure in NICU[1,3]. Preterm and ill infants are at an increased risk of peripheral intravenous catheter (PIVC) related complications[1,3–6]. In part, this is due to immature skin anatomy and physiology, immature immune system, and smaller fragile blood vessels[3–6]. When making decisions about vascular access requirements, a '5Rs' mnemonic (after Steere et al.[7]) can be referred to as an aid to supporting patient safety and wellbeing.

PIVC related complications are a major clinical concern in NICUs. Frequently encountered complications are infiltration and extravasation (PIVIE), leakage, occlusion, thrombosis, phlebitis, infection, and dislodgment or accidental removal[1,4,8–12]. According to Pettit[13], the incidence of complications has remained constant over recent decades irrespective of clinical innovations and changes in practice. Overall, the risk for a PIVC related complication in this patient population is reported as up to 75%[1,5,6,9,12,14]. Of particular concern is the risk of PIVIE which according to several sources is high in the neonatal population, having an incidence of around 65%[1,4,9,13]. Infection rates are highly variable, but have been documented as between 2 to 49 incidents per 1000 catheter days[15].

Extrinsic modifiable factors influence PIVC dwell time, such as clinician training, exposure, experience, choice of the optimal PIVC for the right patient for the right therapy, site selection and preparation, insertion technology, maintenance care bundles, stabilization materials and dressings[3–5,16]. Recent evidence from large scale studies in neonatal populations regarding factors influencing PIVC is lacking and absent for Middle Eastern settings and contexts. The current study aims to identify and evaluate the relationships between unmodifiable and potentially modifiable factors with the presence of PIVC related complications.

METHODS

Design and setting

This retrospective observational study uses routinely collected anonymized data from January 2019 to July 2020. The outcome of the study was the occurrence of any complication in relation to PIVC use, leading to unplanned removal of the device before completion of the intended intravenous therapy. The study was carried out on the NICU (112 cots) of the Women's Wellness and Research Centre (WWRC) of Hamad Medical Corporation (HMC), Doha, Qatar.

Participants and sample size

Infants who were admitted to the NICU and who required intravenous therapy were included in this study. Participants were excluded from the sample if the data collection was incomplete or related to the use of other devices (centrally inserted central catheters or peripherally inserted central catheters).

Procedure

Peripheral intravenous cannulation was performed according to hospital policy based on international guidelines[17]. In the study setting, peripheral intravenous cannulation is routinely performed by nurses from the NICU vascular access team (VAT). Proactive

choices to prevent patients from running out of veins and being labeled as a difficult vascular access patient are key in the selection of cannulation site and intravenous catheter[7]. For that reason, saphenous and elbow veins generally are avoided for cannulation[17]. The selection of suitable veins was done using the VeinViewer® (Christie Medical Holdings Inc., Lake Mary, FL, USA). Vein length, valves, and potential for the vein to fill and empty itself were prior assessed using a standardized approach to appraisal of the potential site. Short peripheral intravenous catheters were used if therapy was predicted for up to two days, including a 26 or 24-gauge Neoflon™ Pro (Becton Dickinson Infusion Therapy, Sandy, UT, USA) or a 26-gauge SuperCath™ Safety (ICU Medical, San Clemente, CA, USA). Extended 22-gauge peripheral intravenous catheters were inserted when duration of therapy was expected to last for 5 days (LeaderFlex, Vygon, Lansdale, PA, USA). In situations where intravenous therapy was expected to last more than 5 days central venous access is preferred. According to hospital protocols, and based on international guidelines, there is no evidence for routine rotation of vascular access devices in the neonatal population[17].

Measurements and data collection

The main outcome was the occurrence of any peripheral intravenous cannulation failure, leading to unplanned removal of the device before completion of the intended intravenous therapy. Patient demographics and baseline data included sex, gestational age at birth in weeks and days, birth weight, and current body weight in grams. Data regarding the procedure of peripheral intravenous cannulation were the date and time

of cannulation, as well as the number of attempts needed to successful cannulation, cannulation side (left or right), extremity of cannulation and the site on the extremity (dorsum of the hand, wrist and lower arm, elbow crease and upper arm, foot, ankle and lower leg, or knee and upper leg), size of device (22, 24, or 26 gauge), the indication for intravenous treatment (intravenous fluids, medications, total parenteral nutrition, blood and blood products, blood extraction, or procedural), the date and time of removal of the PIVC, total dwell time of the PIVC in hours (calculated as the removal date and time minus the insertion date and time), and the reason for removal of the PIVC (therapy completed and elective removal, PIVIE, phlebitis, occlusion, dislodgement and accidental removal, discoloration, patient transferred or expired). Furthermore, additional data points included the use of catheter securement glue, application of ivWatch® (ivWatch LLC., Newport News, VA, USA), if the touch-look-compare observation tool was used, and calculation of the PIVIE Severity Score in percentages[18,19]. The ivWatch® was introduced into use in January 2020 and applied since then with infants weighing more than 1000 grams.

Statistical analyses

Descriptive statistics were used to summarize the outcomes with a mean and its standard deviation or median and its range for continuous variables regarding its normal distribution, and absolute numbers with percentage for discrete variables. The assumption of normal distribution was proved with Kolmogorov-Smirnof testing. Differences regarding outcomes and measurements were demonstrated by using the

χ^2-test, Mann-Whitney *U* test, or unpaired samples *t* test, as appropriate. Stepwise Cox' hazard regression analyses were used to provide correlations between variables regarding the outcome of this study and obtain its odds ratio with 95% confidence interval. Items with a significant relationship ($P<0.01$) to the outcome of this study from a univariate analysis were entered in these analyses. The stepwise method was utilized to remove independent variables that did not make a significant contribution to the primary outcome variable using a backward elimination process based on the Wald statistic and level of significance, with the removal criteria set at $P=0.01$, to obtain a model with a minimal set of variables. Correlation between variables was measured by determining Pearson's or Spearman's ρ, as appropriate. Survival analyses of PIVC in terms of its dwell time were performed by plotting a Kaplan-Meier curve. Differences between survival time of the PIVC according to its reason for premature removal were represented with Log Rank (Mantel-Cox) χ^2. In addition, Log Rank (Mantel-Cox) χ^2 analyses were used for all comparisons regarding the different outcome measures on device dwell-time. A $P<0.05$ was denoted to be statistically significant throughout this study. SPSS (version 25.0; SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Ethics approval statement

The study protocol (MRC-01-20-594) was approved by the local institution review body (IRB). As the data source was anonymized, the local IRB deemed that participant consent was not feasible nor required as they determined the study a 'chart review'.

Participants and their parents were not involved in the design, conduct or reporting of this study.

Patient and public involvement

Study outcome measurements were based on recent literature and after a brainstorm session with the researchers. The study did not involve any patient nor member of the public in the conception, design and development of the study protocol. They were not also involved in data acquisition, analyses, interpretation and development of this manuscript.

RESULTS

In total, data on 15087 cannulation events in neonates was collected during the study period, of which data of 2109 participants were removed due to incompleteness, including failure to insert. The final database included 12978 participants, with 7695 (59%) being of male sex. Mean gestational age was 34+6 (23 to 43) weeks. Current age in days after birth was 9 (0 to 29) days at the time that peripheral intravenous cannulation was performed. Mean weight at birth was 2334 ±975 grams, with a mean current weight of 2410 ±931 grams at the time of cannulation.

Successful peripheral intravenous cannulation at the first attempt was obtained in 8481 participants (65%). 24% needed two attempts, 8%, 2% needed three attempts and a small number, under senior clinician oversight needed more attempts to successfully insert a PIVC. Throughout the study were 19329 insertion attempts performed to create peripheral intravenous access. Data regarding the procedure of peripheral intravenous cannulation is summarized in Table 1.

Failure of the PIVC, resulting in premature removal, occurred in 7627 participants (59%). In 5145 participants (40%), the PIVC was removed after completion of intravenous therapy. In 142 cases (1%) was the participant transferred or expired (administrative censoring). A mean dwell time of 36 ±28 hours was recorded in participants with no complications, whereas the mean dwell time was 31 ±23 hours in participants with an indication for premature removal of the PIVC (P<0.001,

χ^2=5850.77, df=1). Subsequently, there was a correlation between dwell times and the occurrence of a PIVC related complication (*P*<0.001, ρ=-0.099). The overall PIVC complication rate was 18 per 1000 catheter days. PIVIE was the most frequently observed complication throughout the studied cohort, with a relative risk (RR) for device failure of 3.14 (3.04 to 3.25). Additional information according to the reason for removal of the PIVC is shown in Table 2.

Total dwell time of the device in each participant until its moment of removal is represented in Figure 1. 50% of PIVC were removed within the first 38 hours. Dwell times differed regarding the reason for removal or the kind of PIVC related complication (*P*<0.001, χ^2=76.83, df=4).

As shown in Table 3, twelve variables had a significant relation with the outcome of interest in the univariate logistic analyses, resulting in premature removal of the device. These items were used for multivariate analyses, resulting in a smallest set of five variables correlating with the outcome of this study (Table 4).

A lower weight at birth (odds ratio =0.23, 0.20 to 0.28, *P*<0.001) and a lower current body weight (odds ratio =1.06, 1.03 to 1.10, *P*=0.018) resulted in an increased risk for PIVC related complications. Cannulation on the hand showed the lowest complication rate (57%), whereas most complications were reported after cannulation on the ankle or lower leg (72%) (*P*<0.001, χ^2=112.65, df=6). Inserting a 22-gauged device resulted in 77% of cases in a complication, cannulation with a 26-gauged catheter led to complications in 49% of insertions (*P*=0.001, χ^2=17.04, df=3). If TPN was the indication for starting up intravenous treatment, 64% resulted in premature removal of the device,

whereas only 18% of insertion resulted in a complication if cannulation was performed per procedure and elective (P<0.001, χ^2=288.33, df=4). Cannulation site (odds ratio =1.23, 1.16 to 1.30, P<0.001), the inserted device (odds ratio =0.89, 0.84 to 0.94, P<0.001) and the indication for intravenous treatment (odds ratio =0.76, 0.73 to 0.79, P<0.001) were modifiable factors.

The PIVIE Severity Score was higher in participants with an indication for premature removal of the device (13.1 ±8.6) when compared to those without a VAD related complication (0.8 ±4.1) (P<0.001, t=-25.409). PIVIE Severity Scores were in increased in participants suffering from PIVIE (13.8 ±8.0) and phlebitis (12.9 ±9.9). Furthermore, a correlation between the PIVIE Severity Score and device dwell time could be obtained (P<0.001, ρ=-0.122). The ivWatch® was applied in 12% of participants, of which 63% suffered from premature removal. The added value of this device resulted in a sensitivity of 57% and a specificity of 56% (P<0.001, χ^2=54.165, df=1). Catheter dwell times of 38 ±26 were seen after the application of ivWatch®, which did not differ from dwell times of 31 ±25 in participants in whom the technique was not used (P<0.001, χ^2=45.31, df=1). Despite, a correlation between the application of the ivWatch® and device dwell times could not be obtained (P=0.705, ρ=-0.006). The touch-look-compare observation tool was applied in 67% of cases and detected complications in 61% of participants with an event (P=0.002, χ^2=9.975, df=1). The use of the touch-look-compare observation tool resulted in a sensitivity of 97% and a specificity of 96% and correlated with device dwell time (P=0.001, ρ=-0.032). The use of glue for fixation of the PIVC increased the dwell time to 34 ±25 when compared to

participants in which no glue was used (dwell time of 28 ±18), although the difference was not significant (P=0.623, χ^2=0.24, df=1). A correlation could not be seen between the use of glue and PIVC dwell times (P=0.025, ρ=-0.106).

DISCUSSION

The incidence of VAD failure is high in clinical practice, which negatively affects a neonate's comfort and outcome[20,21]. Failure of peripheral inserted PIVC, resulting in premature removal, occurred in 51% of participants, with a complication rate of 18 per 1000 device days. The most frequently reported complications were PIVIE and phlebitis. The risk for complications was increased in participants with a lower weight at birth and current body weight. Furthermore, the cannulation site, size and type of device, and the indication for intravenous treatment affected the risk for failure as well.

Although this study provides information on the risk of complications regarding peripheral intravenous cannulation in neonates, majority of it was reported in many articles. Nonetheless, to the best of our knowledge, a study including as many patients as the current study does was never published before on this topic.

Peripheral intravenous catheters are often the primary and most commonly inserted devices used to obtain vascular access during hospitalization[20]. The incidence of device failure in the current study is slightly higher when compared to the 34% pooled incidence of failure in the recently published meta-analyses by Indarwati et al.[22]. It is difficult to give an unambiguous clarification for this, although the pattern of complications and their relative incidence does match.

PIVIE was the most common complication in infants admitted to the NICU, with an incidence of 34% in the current study. PIVIE is defined as an unintended infusion of

fluids and/or medication in the surrounding tissue, in which infiltration is the infusion of non-vesicant fluids or medication and extravasation infusion of vesicants into surrounding tissues[5]. The determination of PIVIE can be subjective, making it hard to compare the results of different studies. However, standardized training of a dedicated VAT and routine review of scores can improve consensus and reduce subjectivity. The incidence of infiltration reported elsewhere ranges from 6% to 87%, and the incidence of extravasation between 2% and 77%[22]. The use of the infiltration/extravasation staging instrument, as developed by Montgomery et al.[23], could accomplish consensus on the definition of the condition and its severity[5]. An explanation for the non-standard use of this instrument may be that it has not been externally validated.

Phlebitis (inflammation of the venous wall) can cause discomfort and tissue damage. The incidence was 10% in the current study which is broadly in accord with other reports[22–27]. According to Arias-Fernandez et al.[28], assessment of phlebitis is difficult because the consensus for the diagnosis is low. Furthermore, a lack of consensus on phlebitis measures has likely contributed to disparities in reported phlebitis incidence[29].

Several tools are used in clinical practice to reduce the risk or severity for premature failure of PIVCs due to device related complications. The touch-look-compare observation tool was developed at Cincinnati Children's Hospital Medical Center to reduce peripheral intravenous infiltration and extravasation injuries[18]. This documented methodical hourly assessment of patients with a PIVC can help practitioners' standardize their practice and reduce variations in quality of care[18]. Our study showed highly discriminative effects of the touch-look-compare observation tool

based on high sensitivity and specificity, which was denoted as the most decisive tool in detecting device related complications in earlier. Routine observations by combining the touch-look-compare observation tool and the PIVIE Severity Scoring instrument seems to result in the most optimal situation regarding the early detection of complications.

It is known that the preferred cannulation site is the dorsal hand, on which fewer attempts were required for successful cannulation, with fewer complications and extended dwell times[14]. This is in accordance with the results of the current study. Moreover, phlebitis caused by mechanical irritation due to the device is thought to be an important factor for failure[21]. Fixation of the device after insertion with glue increases the stability of the device. Despite no significance could be obtained, dwell times were increased after using glue in this study. Highest incidence of premature removal of the device was seen with a 22-gauged device. Insertion of a 26-gauged catheter resulted in the lowest incidence of complications. Notwithstanding, most participants in this study received a 26-gauged device, possibly leading to a distorting result. To minimize the risk for phlebitis, the smallest gauged catheter possible should be inserted and the use of extension tubes as an accessory to the device should be avoided[27].

Preterm infants are extra sensitive to the development of PIVIE and phlebitis due to their immature immune systems[22,30]. Beall et al.[30] concluded that the inadequate anti-inflammatory response may fail to release free radical scavengers leading to endothelial apoptosis and injury of cell membranes and vessels. To add to this, it is thought that medications or fluids with a higher osmolality increases the risk for

extravasation by irritating the endothelial lining of the vein[22]. Early detection of signs and symptoms correlating positively with PIVC complications is crucial in limiting the risk for failure of the device. Assessing pain accurately in preverbal infants is challenging[31]. Moreover, additional occlusive fixtures and bandages to secure the device add limits to identifying early stages of complications, and thus timely cessation of therapy and treatment to minimize harm[22,31]. The incidence of complications could likely be reduced with consistent and quality insertion and maintenance practices. The Infusion Nurses Society provides specific recommendations for newborn infants offering further specific guidelines for insertion and management practice[17].

Limitations

The current study was based on a retrospective collected dataset. In contrast to randomized studies, the method creates a risk for selection bias. In the present study every infant with a PIVC was included in order to minimize the risk of selection bias. In addition, this current study was carried out according to the STROBE statement[32]. Inter-rater variability might have affected the results, however, our use of standardized education and training and limiting vascular access to a small team (the VAT) will mitigate this variability in the data. Nonetheless, future research should focus on the development and validation of decisive tools and their integration with emerging technologies to identify complications early.

CONCLUSION AND RELEVANT IMPLICATIONS

Most infants experienced a vascular access related complication. Five variables were identified as factors affecting PIVC dwell time in patients admitted to the NICU. These factors include a lower weight at birth and current body weight, the cannulation site, size and type of device and the indication for intravenous treatment affected the risk for failure as well. The PIVC complication rate was 18 per 1000 catheter days in the current study. The risk for the development of a PIVC related complication, leading to premature removal of the device, increased with extended dwell times. It seems that when a PIVC is inserted it is not the question of if the infant will have a complication, but only a matter of when. The most frequently observed complication in the neonatal population is a PIVIE, with a RR of 3.14 (3.04 to 3.25). Consequently, we argue that PIVC should be used judiciously, and thought given prior to their use as to whether alternate means of IV access might be more appropriate.

ADDITIONAL INFORMATION

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designed the data collection instruments, collected data, and reviewed and revised the manuscript. Krisha L.P. Garcia designed the data collection instruments, collected data, and reviewed and revised the manuscript. Fredericus H.J. van Loon conceptualized and designed the study, carried out the initial analyses, and critically reviewed the manuscript for important intellectual content and revised the manuscript.

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Table 1: Procedural peripheral intravenous cannulation data

Factor	Description	Total cohort *N = 12978*	Successful first attempt *N = 8481*	Unsuccessful first attempt *N = 4497*	*P*-value
Side of cannulation	*Left*	7120 (55%)	4794 (57%)	2326 (52%)	<0.001
	Right	5854 (45%)	3684 (43%)	2170 (48%)	
Site of cannulation on the selected extremity	*Hand*	10512 (81%)	7078 (83%)	3434 (76%)	<0.001
	Wrist/ lower arm	459 (4%)	240 (3%)	219 (5%)	
	Elbow/ upper arm	61 (<1%)	33 (1%)	28 (1%)	
	Foot	1774 (14%)	1025 (12%)	749 (17%)	
	Ankle/ lower leg	119 (1%)	78 (1%)	41 (1%)	
	Knee/ upper leg	50 (<1%)	25 (<1%)	25 (<1%)	
	Scalp	2 (<1%)	1 (<1%)	1 (<1%)	
Size of the inserted catheter	*26 gauge*	12403 (96%)	8090 (96%)	4313 (96%)	<0.001
	24 gauge	141 (1%)	97 (1%)	44 (1%)	
	22 gauge	434 (3%)	294 (3%)	140 (3%)	
Indication for intravenous treatment	*IV fluids/ medications*	7283 (56%)	4781 (56%)	2502 (56%)	<0.001
	IV fluids/ TPN	4330 (33%)	2844 (34%)	1486 (33%)	
	Blood and blood products	482 (4%)	285 (3%)	197 (4%)	
	Blood extraction	708 (5%)	455 (5%)	253 (6%)	

Procedure	175 (2%)	116 (2%)	59 (1%)

Data is represented as absolute number and percentages, which were calculated as a proportion within in the cell. IV = intravenous, TPN = total parenteral nutrition.

Table 2: Data representing the reason for removal of the peripheral intravenous catheter.

Factor	Description	Device dwell time (hours)	Total cohort *N = 12914*
Reason for removal of the VAD	*Therapy completed/ elective*	36 ±28	5145 (40%)
	PIVIE	31 ±24	5159 (40%)
	Phlebitis	29 ±19	1590 (12%)
	Occlusion	41 ±29	527 (4%)
	Dislodgement/ accidental removal	23 ±25	286 (2%)
	Swelling or discoloration	22 ±20	65 (1%)
	Administrative censoring	17 ±26	142 (1%)

Data is represented as mean and its standard deviation or as absolute number and percentages, which were calculated as a proportion within the cell. Device dwell time is represented in hours. VAD = vascular access device, PIVIE = peripheral intravenous intravasation and extravasation. Data of 64 participants is missing.

Table 3: Univariate Cox' hazard regression analyses with factors affecting the risk for failure of peripheral intravenous access devices.

Factor	β	Odds ratio	95% confidence interval	*P* value
Sex of the participant	0.025	1.03	0.98 – 1.07	0.292
Duration of gestation in weeks	-0.014	0.98	0.98 – 0.99	<0.001
Current age in days since gestation	-0.501	0.61	0.37 – 0.99	0.047
Weight at birth in grams	-0.072	0.93	0.88 – 0.97	0.002
Current weight in grams	0.037	1.04	1.01 – 1.07	0.010
Successful first attempt of cannulation	0.006	1.01	0.95 – 1.06	0.810
Number of attempts to successful cannulation	-0.005	0.99	0.96 – 1.03	0.758
Side of cannulation	0.161	1.18	1.12 – 1.23	<0.001
Site of cannulation on the extremity	0.079	1.08	1.05 – 1.11	<0.001
Size of the inserted intravenous catheter	-0.080	0.92	0.89 – 0.96	<0.001
Indication for intravenous treatment	-0.292	0.75	0.72 – 0.78	<0.001
Time of the device in situ	-0.499	0.61	0.56 – 0.65	<0.001
Application of TLC observation	0.265	1.30	1.13 – 1.50	<0.001
PIVIE Severity Score	0.023	1.02	1.01 – 1.03	<0.001
Application of the ivWatch®	0.199	1.22	1.12 – 1.33	<0.001

Application of device fixation glue	-0.118	0.89	0.64 – 1.23	0.477

TLC = touch-look-compare*, PIVIE = peripheral intravenous infiltration and extravasation.*

Table 4: Multivariate Cox' hazard regression analyses with factors affecting the risk for failure of peripheral intravenous access devices.

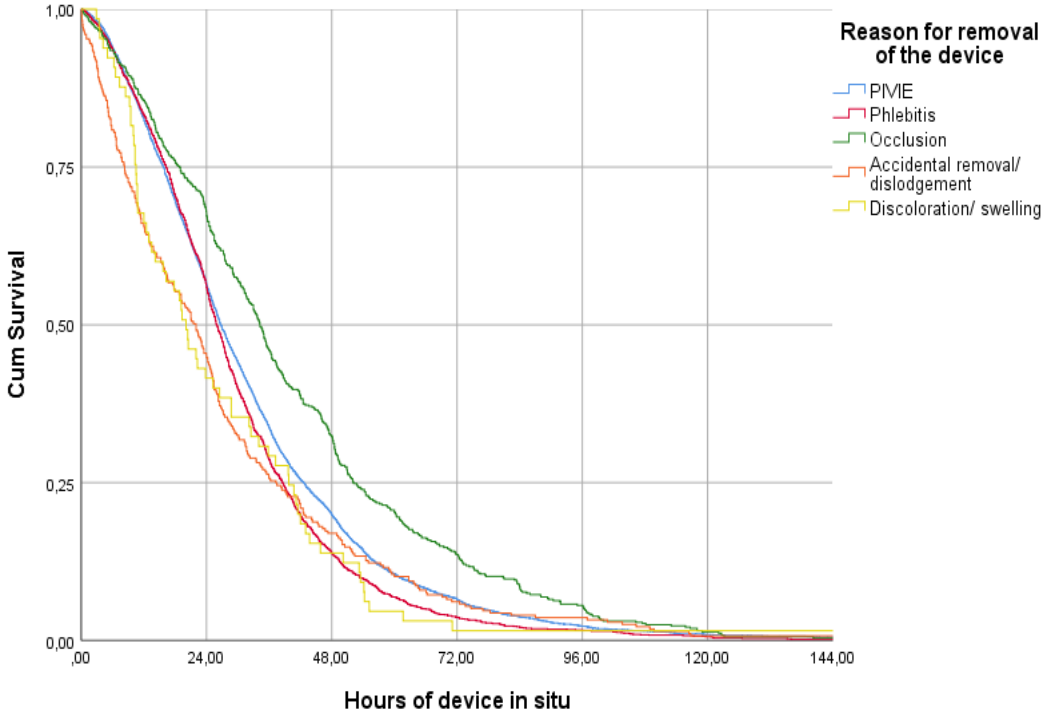
Factor	β	Odds ratio	95% confidence interval	*P* value
Weight at birth in grams	-1.452	0.23	0.20 – 0.28	<0.001
Current weight in grams	0.062	1.06	1.03 – 1.10	0.018
Site of cannulation on the extremity	0.207	1.23	1.16 – 1.30	<0.001
Size of the inserted intravenous catheter	-0.119	0.89	0.84 – 0.94	<0.001
Indication for intravenous treatment	-0.280	0.76	0.73 – 0.79	<0.001

Figure 1: Kaplan-Meier survival analyses for peripheral intravenous catheters.

Intravenous catheters were removed after the occurrence of a complication, of which dwell times were compared between the type of complications as measured in this study. PIVIE = peripheral intravenous infiltration and extravasation.

* Figure was attached as separated file.

Figure 1: Kaplan-Meier survival analyses for peripheral intravenous catheters.



Intravenous catheters were removed after the occurrence of a complication, of which dwell times were compared between the type of complications as measured in this study. PIVIE = peripheral intravenous infiltration and extravasation.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**3**
Objectives	3	State specific objectives, including any prespecified hypotheses	**3**
Methods			
Study design	4	Present key elements of study design early in the paper	**4**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**4**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	**4**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	**4**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**5**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**5**
Bias	9	Describe any efforts to address potential sources of bias	**5**
Study size	10	Explain how the study size was arrived at	**5**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**5,6**
		(*b*) Describe any methods used to examine subgroups and interactions	**5,6**
		(*c*) Explain how missing data were addressed	**5,6**
		(*d*) If applicable, explain how loss to follow-up was addressed	**5,6**
		(*e*) Describe any sensitivity analyses	**5,6**
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**7,8**
		(b) Give reasons for non-participation at each stage	**7,8**
		(c) Consider use of a flow diagram	**7,8**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**7,8**
		(b) Indicate number of participants with missing data for each variable of interest	**7,8**
		(c) Summarise follow-up time (eg, average and total amount)	**7,8**
Outcome data	15*	Report numbers of outcome events or summary measures over time	**7,8**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**7,8**
		(*b*) Report category boundaries when continuous variables were categorized	**7,8**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**7,8**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**7,8**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**9**
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**11**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**11**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**13**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Evaluation of unmodifiable and potentially modifiable factors affecting peripheral intravenous device related complications in neonates: a retrospective observational study.

Matheus F.P.T. van Rens[1], Kevin Hugill[1], Mohamad A. Mahmah[1], Mohammad A.A. Bayoumi[1], Airene L.V. Francia[1], Krisha L.P. Garcia[1], Fredericus H.J. van Loon[2,3].

Affiliations: [1] Neonatal Intensive Care Unit, Women's Wellness and Research Center, Hamad Medical Corporation, Doha, Qatar; [2] Department of Science and Technology in Perioperative Nursing, Fontys University of Applied Sciences, Eindhoven, The Netherlands; and [3] Department of Anesthesiology, Intensive Care and Pain Medicine Catharina Hospital, Eindhoven, The Netherlands.

Address correspondence to: F.H.J. van Loon. Post to: Fontys University of Applied Sciences, Department of Technical and Anesthesia Nursing Sciences, Ds. Th. Fliednerstraat 2, Building TF, 5631 BN Eindhoven, The Netherlands. Email to: rick.vanloon@fontys.nl.

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ABSTRACT

Objectives: Infants in neonatal units benefit from dependable peripheral intravenous access. However, peripheral intravenous access exposes infants to high rates of clinically minor and serious complications. Despite this, little is known about the interplay of risk factors. The aim of this study was to assess the incidence and evaluate the interactions of risk factors on the occurrence of peripheral intravenous complications in a neonatal population. **Design:** This was a retrospective observational study. **Setting:** The study was performed on the Neonatal Intensive Care Unit (NICU) of the Women's Wellness and Research Centre, Hamad Medical Corporation, Qatar as a single site study. **Participants:** This study included 12978 neonates who required intravenous therapy. **Outcome measurements:** The main outcome was the occurrence of any peripheral intravenous cannulation failure, leading to unplanned removal of the device before completion of the intended intravenous therapy. **Results:** A mean dwell time of 36 ±28 hours was recorded in participants with no complications, whereas the mean dwell time was 31 ±23 hours in participants with an indication for premature removal of the peripheral intravenous catheter (P<0.001, t=11.35). Unplanned removal occurred in 59% of cases, the overall complication rate was 18 per 1000 catheter days. Unmodifiable factors affecting peripheral intravenous catheter dwell time include lower birth (hazard ratio =0.23, 0.20 to 0.28, P<0.001) and current body weight (hazard ratio =1.06, 1.03 to 1.10, P=0.018). Cannulation site (hazard ratio =1.23, 1.16 to 1.30, P<0.001), the inserted device (hazard ratio =0.89, 0.84 to 0.94, P<0.001) and the

indication for intravenous treatment (hazard ratio =0.76, 0.73 to 0.79, P<0.001) were modifiable factors. **Conclusions:** Most infants experienced a vascular access related complication. Given the high complication rate, peripheral intravenous catheters should be used judiciously, and thought given prior to their use as to whether alternate means of intravenous access might be more appropriate.

Strengths and limitations of this study

- This was an observational study including a large sample of 12978 neonates.
- This study provides information on the risk of complications regarding peripheral intravenous cannulation in neonates.
- This study is based on retrospective analyses of collected data.

INTRODUCTION

Providing reliable vascular access in the neonatal intensive care unit (NICU) is essential to administer nutrition, fluids, medication, and blood products[1]. Critically ill and preterm infants benefit from early intravenous therapy[2]. Currently the main intravenous (IV) vascular access routes, are via peripheral and central veins. Peripheral intravenous cannulation is the most frequently performed procedure in NICU[1,3]. Preterm and ill infants are at an increased risk of peripheral intravenous catheter (PIVC) related complications[1,3–6]. In part, this is due to immature skin anatomy and physiology, immature immune system, and smaller fragile blood vessels[3–6]. When making decisions about vascular access requirements, a '5Rs' mnemonic (after Steere et al.[7]) can be referred to as an aid to supporting patient safety and wellbeing.

PIVC related complications are a major clinical concern in NICUs. Frequently encountered complications are infiltration and extravasation (PIVIE), leakage, occlusion, thrombosis, phlebitis, infection, and dislodgment or accidental removal[1,4,8–12]. According to Pettit[13], the incidence of complications has remained constant over recent decades irrespective of clinical innovations and changes in practice. Overall, the risk for a PIVC related complication in this patient population is reported as up to 75%[1,5,6,9,12,14]. Of particular concern is the risk of PIVIE which according to several sources is high in the neonatal population, having an incidence of around 65%[1,4,9,13]. Infection rates are highly variable, but have been documented as between 2 to 49 incidents per 1000 catheter days[15].

Extrinsic modifiable factors influence PIVC dwell time, such as clinician training, exposure, experience, choice of the optimal PIVC for the right patient for the right therapy, site selection and preparation, insertion technology, maintenance care bundles, stabilization materials and dressings[3–5,16]. Recent evidence from large scale studies in neonatal populations regarding factors influencing PIVC is lacking and absent for Middle Eastern settings and contexts. The current study aims to identify and evaluate the relationships between unmodifiable and potentially modifiable factors with the presence of PIVC related complications.

METHODS

Design and setting

This retrospective observational study uses routinely collected anonymized data from January 2019 to July 2020. The outcome of the study was the occurrence of any complication in relation to PIVC use, leading to unplanned removal of the device before completion of the intended intravenous therapy. The study was carried out on the NICU (112 cots) of the Women's Wellness and Research Centre (WWRC) of Hamad Medical Corporation (HMC), Doha, Qatar.

Participants and sample size

Infants who were admitted to the NICU and who required intravenous therapy were included in this study. Participants were excluded from the sample if the data collection was incomplete or related to the use of other devices (centrally inserted central catheters or peripherally inserted central catheters).

Procedure

Peripheral intravenous cannulation was performed according to hospital policy based on international guidelines[17]. In the study setting, peripheral intravenous cannulation is routinely performed by nurses from the NICU vascular access team (VAT). Proactive

choices to prevent patients from running out of veins and being labeled as a difficult vascular access patient are key in the selection of cannulation site and intravenous catheter[7]. For that reason, saphenous and elbow veins generally are avoided for cannulation[17]. The selection of suitable veins was done using the VeinViewer® (Christie Medical Holdings Inc., Lake Mary, FL, USA). Vein length, valves, and potential for the vein to fill and empty itself were prior assessed using a standardized approach to appraisal of the potential site. Short peripheral intravenous catheters were used if therapy was predicted for up to two days, including a 26 or 24-gauge Neoflon™ Pro (Becton Dickinson Infusion Therapy, Sandy, UT, USA) or a 26-gauge SuperCath™ Safety (ICU Medical, San Clemente, CA, USA). Extended 22-gauge peripheral intravenous catheters were inserted when duration of therapy was expected to last for 5 days (LeaderFlex, Vygon, Lansdale, PA, USA). In situations where intravenous therapy was expected to last more than 5 days central venous access is preferred. According to hospital protocols, and based on international guidelines, there is no evidence for routine rotation of vascular access devices in the neonatal population[17].

Measurements and data collection

The main outcome was the occurrence of any peripheral intravenous cannulation failure, leading to unplanned removal of the device before completion of the intended intravenous therapy. Patient demographics and baseline data included sex, gestational age at birth in weeks and days, birth weight, and current body weight in grams. Data regarding the procedure of peripheral intravenous cannulation were the date and time

of cannulation, as well as the number of attempts needed to successful cannulation, cannulation side (left or right), extremity of cannulation and the site on the extremity (dorsum of the hand, wrist and lower arm, elbow crease and upper arm, foot, ankle and lower leg, or knee and upper leg), size of device (22, 24, or 26 gauge), the indication for intravenous treatment (intravenous fluids, medications, total parenteral nutrition, blood and blood products, blood extraction, or procedural), the date and time of removal of the PIVC, total dwell time of the PIVC in hours (calculated as the removal date and time minus the insertion date and time), and the reason for removal of the PIVC (therapy completed and elective removal, PIVIE, phlebitis, occlusion, dislodgement and accidental removal, discoloration, patient transferred or expired). Furthermore, additional data points included the use of catheter securement glue, application of ivWatch® (ivWatch LLC., Newport News, VA, USA), if the touch-look-compare observation tool was used, and calculation of the PIVIE Severity Score in percentages[18,19]. The ivWatch® was introduced into use in January 2020 and applied since then with infants weighing more than 1000 grams.

Statistical analyses

Descriptive statistics were used to summarize the outcomes with a mean and its standard deviation or median and its range for continuous variables regarding its normal distribution, and absolute numbers with percentage for discrete variables. The assumption of normal distribution was proved with Kolmogorov-Smirnof testing. Differences regarding outcomes and measurements were demonstrated by using the

χ^2-test, Mann-Whitney *U* test, or unpaired samples *t* test, as appropriate. Stepwise Cox' hazard regression analyses were used to provide correlations between variables regarding the outcome of this study and obtain its odds ratio with 95% confidence interval. Items with a significant relationship ($P<0.01$) to the outcome of this study from a univariate analysis were entered in these analyses. The stepwise method was utilized to remove independent variables that did not make a significant contribution to the primary outcome variable using a backward elimination process based on the Wald statistic and level of significance, with the removal criteria set at $P=0.01$, to obtain a model with a minimal set of variables. Correlation between variables was measured by determining Pearson's or Spearman's ρ, as appropriate. Survival analyses of PIVC in terms of its dwell time were performed by plotting a Kaplan-Meier curve. Differences between survival time of the PIVC according to its reason for premature removal were represented with Log Rank (Mantel-Cox) χ^2. In addition, Log Rank (Mantel-Cox) χ^2 analyses were used for all comparisons regarding the different outcome measures on device dwell-time. A $P<0.05$ was denoted to be statistically significant throughout this study. SPSS (version 25.0; SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Ethics approval statement

The study protocol (MRC-01-20-594) was approved by the local institution review body (IRB). As the data source was anonymized, the local IRB deemed that participant consent was not feasible nor required as they determined the study a 'chart review'.

Participants and their parents were not involved in the design, conduct or reporting of this study.

Patient and public involvement

Study outcome measurements were based on recent literature and after a brainstorm session with the researchers. The study did not involve any patient nor member of the public in the conception, design and development of the study protocol. They were not also involved in data acquisition, analyses, interpretation and development of this manuscript.

RESULTS

In total, data on 15087 cannulation events in neonates was collected during the study period, of which data of 2109 participants were removed due to incompleteness, including failure to insert. The final database included 12978 participants, with 7695 (59%) being of male sex. Mean gestational age was 34+6 (23 to 43) weeks. Current age in days after birth was 9 (0 to 29) days at the time that peripheral intravenous cannulation was performed. Mean weight at birth was 2334 ±975 grams, with a mean current weight of 2410 ±931 grams at the time of cannulation.

Successful peripheral intravenous cannulation at the first attempt was obtained in 8481 participants (65%). 24% needed two attempts, 8%, 2% needed three attempts and a small number, under senior clinician oversight needed more attempts to successfully insert a PIVC. Throughout the study were 19329 insertion attempts performed to create peripheral intravenous access. Data regarding the procedure of peripheral intravenous cannulation is summarized in Table 1.

Failure of the PIVC, resulting in premature removal, occurred in 7627 participants (59%). In 5145 participants (40%), the PIVC was removed after completion of intravenous therapy. In 142 cases (1%) was the participant transferred or expired (administrative censoring). A mean dwell time of 36 ±28 hours was recorded in participants with no complications, whereas the mean dwell time was 31 ±23 hours in participants with an indication for premature removal of the PIVC (P<0.001,

χ^2=5850.77, df=1). Subsequently, there was a correlation between dwell times and the occurrence of a PIVC related complication (*P*<0.001, ρ=-0.099). The overall PIVC complication rate was 18 per 1000 catheter days. PIVIE was the most frequently observed complication throughout the studied cohort, with a relative risk for device failure of 3.14 (3.04 to 3.25). Additional information according to the reason for removal of the PIVC is shown in Table 2.

Total dwell time of the device in each participant until its moment of removal is represented in Figure 1. 50% of PIVC were removed within the first 38 hours. Dwell times differed regarding the reason for removal or the kind of PIVC related complication (*P*<0.001, χ^2=76.83, df=4).

As shown in Table 3, twelve variables had a significant relation with the outcome of interest in the univariate logistic analyses, resulting in premature removal of the device. These items were used for multivariate analyses, resulting in a smallest set of five variables correlating with the outcome of this study (Table 4).

A lower weight at birth (hazard ratio =0.23, 0.20 to 0.28, *P*<0.001) and a lower current body weight (hazard ratio =1.06, 1.03 to 1.10, *P*=0.018) resulted in an increased risk for PIVC related complications. Cannulation on the hand showed the lowest complication rate (57%), whereas most complications were reported after cannulation on the ankle or lower leg (72%) (*P*<0.001, χ^2=112.65, df=6). Inserting a 22-gauged device resulted in 77% of cases in a complication, cannulation with a 26-gauged catheter led to complications in 49% of insertions (*P*=0.001, χ^2=17.04, df=3). If TPN was the indication for starting up intravenous treatment, 64% resulted in premature

removal of the device, whereas only 18% of insertion resulted in a complication if cannulation was performed per procedure and elective (P<0.001, χ^2=288.33, df=4). Cannulation site (hazard ratio =1.23, 1.16 to 1.30, P<0.001), the inserted device (hazard ratio =0.89, 0.84 to 0.94, P<0.001) and the indication for intravenous treatment (hazard ratio =0.76, 0.73 to 0.79, P<0.001) were modifiable factors.

The PIVIE Severity Score was higher in participants with an indication for premature removal of the device (13.1 ±8.6) when compared to those without a VAD related complication (0.8 ±4.1) (P<0.001, t=-25.409). PIVIE Severity Scores were in increased in participants suffering from PIVIE (13.8 ±8.0) and phlebitis (12.9 ±9.9). Furthermore, a correlation between the PIVIE Severity Score and device dwell time could be obtained (P<0.001, ρ=-0.122). The ivWatch® was applied in 12% of participants, of which 63% suffered from premature removal. The added value of this device resulted in a sensitivity of 57% and a specificity of 56% (P<0.001, χ^2=54.165, df=1). Catheter dwell times of 38 ±26 were seen after the application of ivWatch®, which did not differ from dwell times of 31 ±25 in participants in whom the technique was not used (P<0.001, χ^2=45.31, df=1). Despite, a correlation between the application of the ivWatch® and device dwell times could not be obtained (P=0.705, ρ=-0.006). The touch-look-compare observation tool was applied in 67% of cases and detected complications in 61% of participants with an event (P=0.002, χ^2=9.975, df=1). The use of the touch-look-compare observation tool resulted in a sensitivity of 97% and a specificity of 96% and correlated with device dwell time (P=0.001, ρ=-0.032). The use of glue for fixation of the PIVC increased the dwell time to 34 ±25 when compared to

participants in which no glue was used (dwell time of 28 ±18), although the difference was not significant (P=0.623, χ^2=0.24, df=1). A correlation could not be seen between the use of glue and PIVC dwell times (P=0.025, ρ=-0.106).

DISCUSSION

The incidence of VAD failure is high in clinical practice, which negatively affects a neonate's comfort and outcome[20,21]. Failure of peripheral inserted PIVC, resulting in premature removal, occurred in 51% of participants, with a complication rate of 18 per 1000 device days. The most frequently reported complications were PIVIE and phlebitis. The risk for complications was increased in participants with a lower weight at birth and current body weight. Furthermore, the cannulation site, size and type of device, and the indication for intravenous treatment affected the risk for failure as well.

Although this study provides information on the risk of complications regarding peripheral intravenous cannulation in neonates, majority of it was reported in many articles. Nonetheless, to the best of our knowledge, a study including as many patients as the current study does was never published before on this topic.

Peripheral intravenous catheters are often the primary and most commonly inserted devices used to obtain vascular access during hospitalization[20]. The incidence of device failure in the current study is slightly higher when compared to the 34% pooled incidence of failure in the recently published meta-analyses by Indarwati et al.[22]. It is difficult to give an unambiguous clarification for this, although the pattern of complications and their relative incidence does match.

PIVIE was the most common complication in infants admitted to the NICU, with an incidence of 34% in the current study. PIVIE is defined as an unintended infusion of

fluids and/or medication in the surrounding tissue, in which infiltration is the infusion of non-vesicant fluids or medication and extravasation infusion of vesicants into surrounding tissues[5]. The determination of PIVIE can be subjective, making it hard to compare the results of different studies. However, standardized training of a dedicated VAT and routine review of scores can improve consensus and reduce subjectivity. The incidence of infiltration reported elsewhere ranges from 6% to 87%, and the incidence of extravasation between 2% and 77%[22]. The use of the infiltration/extravasation staging instrument, as developed by Montgomery et al.[23], could accomplish consensus on the definition of the condition and its severity[5]. An explanation for the non-standard use of this instrument may be that it has not been externally validated.

Phlebitis (inflammation of the venous wall) can cause discomfort and tissue damage. The incidence was 10% in the current study which is broadly in accord with other reports[22–27]. According to Arias-Fernandez et al.[28], assessment of phlebitis is difficult because the consensus for the diagnosis is low. Furthermore, a lack of consensus on phlebitis measures has likely contributed to disparities in reported phlebitis incidence[29].

Several tools are used in clinical practice to reduce the risk or severity for premature failure of PIVCs due to device related complications. The touch-look-compare observation tool was developed at Cincinnati Children's Hospital Medical Center to reduce peripheral intravenous infiltration and extravasation injuries[18]. This documented methodical hourly assessment of patients with a PIVC can help practitioners' standardize their practice and reduce variations in quality of care[18]. Our study showed highly discriminative effects of the touch-look-compare observation tool

based on high sensitivity and specificity, which was denoted as the most decisive tool in detecting device related complications in earlier. Routine observations by combining the touch-look-compare observation tool and the PIVIE Severity Scoring instrument seems to result in the most optimal situation regarding the early detection of complications.

It is known that the preferred cannulation site is the dorsal hand, on which fewer attempts were required for successful cannulation, with fewer complications and extended dwell times[14]. This is in accordance with the results of the current study. Moreover, phlebitis caused by mechanical irritation due to the device is thought to be an important factor for failure[21]. Fixation of the device after insertion with glue increases the stability of the device. Despite no significance could be obtained, dwell times were increased after using glue in this study. Highest incidence of premature removal of the device was seen with a 22-gauged device. Insertion of a 26-gauged catheter resulted in the lowest incidence of complications. Notwithstanding, most participants in this study received a 26-gauged device, possibly leading to a distorting result. To minimize the risk for phlebitis, the smallest gauged catheter possible should be inserted and the use of extension tubes as an accessory to the device should be avoided[27].

Preterm infants are extra sensitive to the development of PIVIE and phlebitis due to their immature immune systems[22,30]. Beall et al.[30] concluded that the inadequate anti-inflammatory response may fail to release free radical scavengers leading to endothelial apoptosis and injury of cell membranes and vessels. To add to this, it is thought that medications or fluids with a higher osmolality increases the risk for

extravasation by irritating the endothelial lining of the vein[22]. Early detection of signs and symptoms correlating positively with PIVC complications is crucial in limiting the risk for failure of the device. Assessing pain accurately in preverbal infants is challenging[31]. Moreover, additional occlusive fixtures and bandages to secure the device add limits to identifying early stages of complications, and thus timely cessation of therapy and treatment to minimize harm[22,31]. The incidence of complications could likely be reduced with consistent and quality insertion and maintenance practices. The Infusion Nurses Society provides specific recommendations for newborn infants offering further specific guidelines for insertion and management practice[17].

Limitations

The current study was based on a retrospective collected dataset. In contrast to randomized studies, the method creates a risk for selection bias. In the present study every infant with a PIVC was included in order to minimize the risk of selection bias. In addition, this current study was carried out according to the STROBE statement[32]. Inter-rater variability might have affected the results, however, our use of standardized education and training and limiting vascular access to a small team (the VAT) will mitigate this variability in the data. Nonetheless, future research should focus on the development and validation of decisive tools and their integration with emerging technologies to identify complications early.

CONCLUSION AND RELEVANT IMPLICATIONS

Most infants experienced a vascular access related complication. Five variables were identified as factors affecting PIVC dwell time in patients admitted to the NICU. These factors include a lower weight at birth and current body weight, the cannulation site, size and type of device and the indication for intravenous treatment affected the risk for failure as well. The PIVC complication rate was 18 per 1000 catheter days in the current study. The risk for the development of a PIVC related complication, leading to premature removal of the device, increased with extended dwell times. It seems that when a PIVC is inserted it is not the question of if the infant will have a complication, but only a matter of when. The most frequently observed complication in the neonatal population is a PIVIE, with a relative risk of 3.14 (3.04 to 3.25). Consequently, we argue that PIVC should be used judiciously, and thought given prior to their use as to whether alternate means of IV access might be more appropriate.

ADDITIONAL INFORMATION

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designed the data collection instruments, collected data, and reviewed and revised the manuscript. Krisha L.P. Garcia designed the data collection instruments, collected data, and reviewed and revised the manuscript. Fredericus H.J. van Loon conceptualized and designed the study, carried out the initial analyses, and critically reviewed the manuscript for important intellectual content and revised the manuscript.

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Table 1: Procedural peripheral intravenous cannulation data

Factor	Description	Total cohort *N = 12978*	Successful first attempt *N = 8481*	Unsuccessful first attempt *N = 4497*	*P*-value
Side of cannulation	*Left*	7120 (55%)	4794 (57%)	2326 (52%)	<0.001
	Right	5854 (45%)	3684 (43%)	2170 (48%)	
Site of cannulation on the selected extremity	*Hand*	10512 (81%)	7078 (83%)	3434 (76%)	<0.001
	Wrist/ lower arm	459 (4%)	240 (3%)	219 (5%)	
	Elbow/ upper arm	61 (<1%)	33 (1%)	28 (1%)	
	Foot	1774 (14%)	1025 (12%)	749 (17%)	
	Ankle/ lower leg	119 (1%)	78 (1%)	41 (1%)	
	Knee/ upper leg	50 (<1%)	25 (<1%)	25 (<1%)	
	Scalp	2 (<1%)	1 (<1%)	1 (<1%)	
Size of the inserted catheter	*26 gauge*	12403 (96%)	8090 (96%)	4313 (96%)	<0.001
	24 gauge	141 (1%)	97 (1%)	44 (1%)	
	22 gauge	434 (3%)	294 (3%)	140 (3%)	
Indication for intravenous treatment	*IV fluids/ medications*	7283 (56%)	4781 (56%)	2502 (56%)	<0.001
	IV fluids/ TPN	4330 (33%)	2844 (34%)	1486 (33%)	
	Blood and blood products	482 (4%)	285 (3%)	197 (4%)	
	Blood extraction	708 (5%)	455 (5%)	253 (6%)	

Procedure	175 (2%)	116 (2%)	59 (1%)

Data is represented as absolute number and percentages, which were calculated as a proportion within in the cell. IV = intravenous, TPN = total parenteral nutrition.

Table 2: Data representing the reason for removal of the peripheral intravenous catheter.

Factor	Description	Device dwell time (hours)	Total cohort *N = 12914*
Reason for removal of the VAD	*Therapy completed/ elective*	36 ±28	5145 (40%)
	PIVIE	31 ±24	5159 (40%)
	Phlebitis	29 ±19	1590 (12%)
	Occlusion	41 ±29	527 (4%)
	Dislodgement/ accidental removal	23 ±25	286 (2%)
	Swelling or discoloration	22 ±20	65 (1%)
	Administrative censoring	17 ±26	142 (1%)

Data is represented as mean and its standard deviation or as absolute number and percentages, which were calculated as a proportion within the cell. Device dwell time is represented in hours. VAD = vascular access device, PIVIE = peripheral intravenous intravasation and extravasation. Data of 64 participants is missing.

Table 3: Univariate Cox' hazard regression analyses with factors affecting the risk for failure of peripheral intravenous access devices.

Factor	β	Hazard ratio	95% confidence interval	*P* value
Sex of the participant	0.025	1.03	0.98 – 1.07	0.292
Duration of gestation in weeks	0.014	0.98	0.98 – 0.99	<0.001
Current age in days since gestation	0.501	0.61	0.37 – 0.99	0.047
Weight at birth in grams	0.072	0.93	0.88 – 0.97	0.002
Current weight in grams	0.037	1.04	1.01 – 1.07	0.010
Successful first attempt of cannulation	0.006	1.01	0.95 – 1.06	0.810
Number of attempts to successful cannulation	0.005	0.99	0.96 – 1.03	0.758
Side of cannulation	0.161	1.18	1.12 – 1.23	<0.001
Site of cannulation on the extremity	0.079	1.08	1.05 – 1.11	<0.001
Size of the inserted intravenous catheter	0.080	0.92	0.89 – 0.96	<0.001
Indication for intravenous treatment	0.292	0.75	0.72 – 0.78	<0.001
Time of the device in situ	0.499	0.61	0.56 – 0.65	<0.001
Application of TLC observation	0.265	1.30	1.13 – 1.50	<0.001
PIVIE Severity Score	0.023	1.02	1.01 – 1.03	<0.001
Application of the ivWatch®	0.199	1.22	1.12 – 1.33	<0.001

Application of device fixation glue	0.118	0.89	0.64 – 1.23	0.477

TLC = touch-look-compare*, PIVIE = peripheral intravenous infiltration and extravasation.*

Table 4: Multivariate Cox' hazard regression analyses with factors affecting the risk for failure of peripheral intravenous access devices.

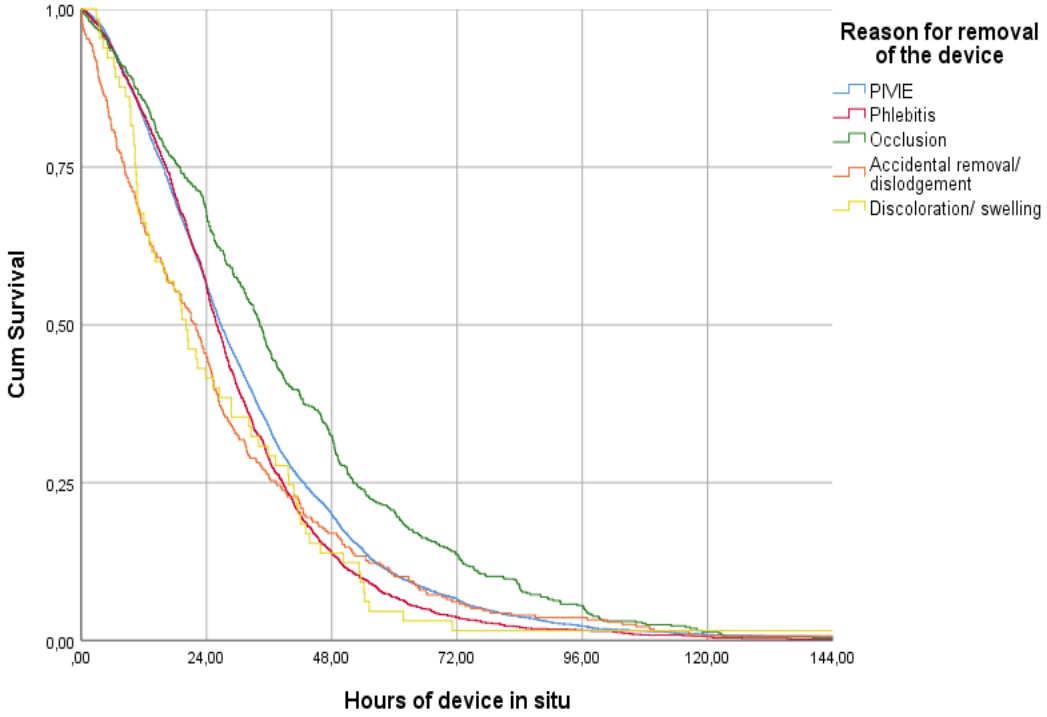
Factor	β	Hazard ratio	95% confidence interval	*P* value
Weight at birth in grams	1.452	0.23	0.20 – 0.28	<0.001
Current weight in grams	0.062	1.06	1.03 – 1.10	0.018
Site of cannulation on the extremity	0.207	1.23	1.16 – 1.30	<0.001
Size of the inserted intravenous catheter	0.119	0.89	0.84 – 0.94	<0.001
Indication for intravenous treatment	0.280	0.76	0.73 – 0.79	<0.001

Figure 1: Kaplan-Meier survival analyses for peripheral intravenous catheters.

Intravenous catheters were removed after the occurrence of a complication, of which dwell times were compared between the type of complications as measured in this study. PIVIE = peripheral intravenous infiltration and extravasation.

* Figure was attached as separated file.

Figure 1: Kaplan-Meier survival analyses for peripheral intravenous catheters.



Intravenous catheters were removed after the occurrence of a complication, of which dwell times were compared between the type of complications as measured in this study. PIVIE = peripheral intravenous infiltration and extravasation.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**3**
Objectives	3	State specific objectives, including any prespecified hypotheses	**3**
Methods			
Study design	4	Present key elements of study design early in the paper	**4**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**4**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	**4**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	**4**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**5**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**5**
Bias	9	Describe any efforts to address potential sources of bias	**5**
Study size	10	Explain how the study size was arrived at	**5**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**5,6**
		(*b*) Describe any methods used to examine subgroups and interactions	**5,6**
		(*c*) Explain how missing data were addressed	**5,6**
		(*d*) If applicable, explain how loss to follow-up was addressed	**5,6**
		(*e*) Describe any sensitivity analyses	**5,6**
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**7,8**
		(b) Give reasons for non-participation at each stage	**7,8**
		(c) Consider use of a flow diagram	**7,8**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**7,8**
		(b) Indicate number of participants with missing data for each variable of interest	**7,8**
		(c) Summarise follow-up time (eg, average and total amount)	**7,8**
Outcome data	15*	Report numbers of outcome events or summary measures over time	**7,8**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**7,8**
		(*b*) Report category boundaries when continuous variables were categorized	**7,8**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**7,8**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**7,8**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**9**
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**11**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**11**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**13**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.