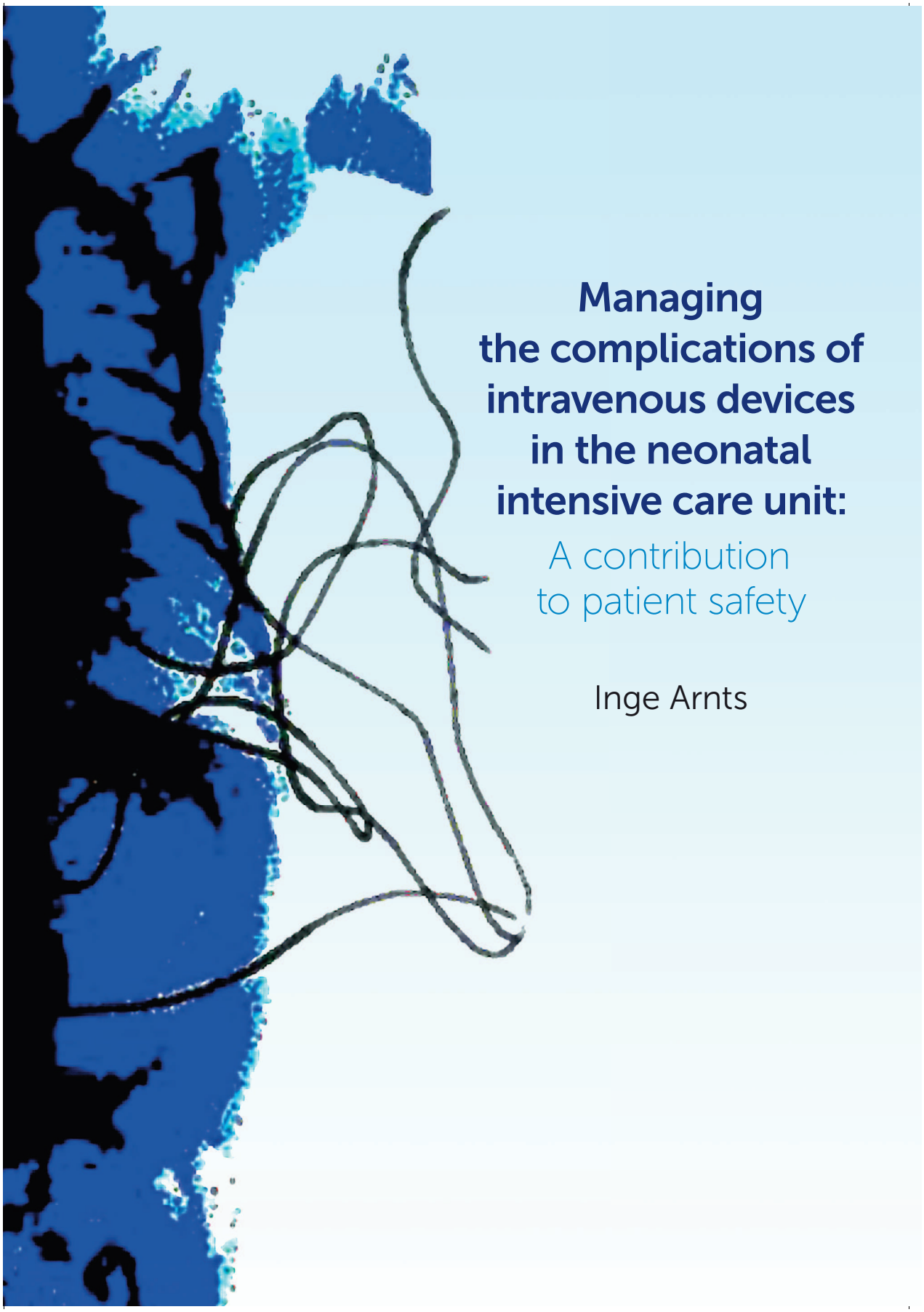

Managing the complications of intravenous devices in the neonatal intensive care unit:

A contribution to patient safety

Inge Arnts

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The studies as presented in this thesis were performed at the Department of Paediatrics, Division of Neonatology, Radboud university medical center, Nijmegen, the Netherlands.

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Yesterday is the past
Tomorrow is a mystery
Today is a gift
That's why they call it... present
Life... treasure it!

Contents

List of abbreviations

CDC	Center for Disease Control and Prevention
CLABSI	Central Line Associated Bloodstream Infection
CI	Confidence Interval
CSEP	Clinical Sepsis
CVC	Central Venous Catheter
ECMO	ExtraCorporeal Membrane Oxygenation
GA	Gestational age
HIT	Heparin Induced Thrombocytopenia
IV	IntraVenous
IVH	Intraventricular Haemorrhage
IVL	IntraVenous Lock
NICU	Neonatal Intensive Care Unit
OR	Odds Ratio
PICC	Peripherally Inserted Central Catheter
PIV	Peripheral Intravenous Catheter
SVC	Surgically inserted central Venous Catheter
TPN	Total Parenteral Nutrition
UAC	Umbilical Arterial Catheter
UC	Umbilical Catheter
UVC	Umbilical venous catheter
VLBW	Very Low Birth Weight

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Introduction and outline of this thesis

Patient safety

The survival of critically ill term and preterm newborns has been improved over the last 30 years as a result of the progress in neonatal medicine and care. However, the treatment of these vulnerable patients in the neonatal intensive care unit (NICU) has become increasingly complex. The increased numbers of often invasive new modalities for treatment and care may potentially compromise patient safety contributing to complications and increased morbidity. Therefore, serious efforts should be made in order to maximize patient safety.

One of the essential treatments in the NICU is the intravenous (IV) administration of total parenteral nutrition (TPN) and medication. Intravenous treatment has been associated with serious complications such as central line associated bloodstream infection (CLABSI), extravasation, thrombophlebitis and thrombosis. These complications result in a greater risk of morbidity. Reduction of complications of IV catheters forms the focus of this thesis.

Intravenous therapy in newborns

In the NICU, IV therapy is an essential part of the care of a newborn (gestational age between 24-42 weeks). The need for indwelling IV catheters to provide therapy is considered standard of care. IV catheters are used to administer continuous TPN and/or medication.

The choice of an appropriate vascular access device in newborns depends on the birth weight, the type of infusate and the expected duration of therapy.

Unfortunately, IV access also increases the risk of complications. Repeated attempts to obtain IV access can disrupt the skin's integrity, thus increasing the risk of systemic infections. Preterm newborns are at an additional risk to develop a systemic infection because of the immature immune system (1). Below we provide a short overview of the different IV access devices used in NICUs.

It is important to choose the best option for each neonate thus aiming to achieve the necessary therapy with the lowest complication risk.

1. Peripheral IV Catheter

The peripheral IV catheter (PIV) is the most commonly used catheter to administer medications with the exception of medication or fluid with high or low pH or hyper-osmolarity which may cause severe damage to small veins (2).

The insertion of a PIV in newborn infants can be difficult. Appropriate veins with sufficient calibre to insert a catheter become less available throughout the hospital stay. Pettit describes a minimum of 2.2 attempts to achieve a successful IV access

(3). In many NICUs only specially trained nurses, neonatologists or residents are allowed to insert a PIV.

Once a PIV is inserted it is desirable that its patency can be maintained as long as possible. Flint et al. published a Cochrane review, in which they compared continuous infusion versus intermittent flushing to maintain patency of PIV. They concluded that intermittent flushing is not associated with a decreased PIV patency or other disadvantages, thus supporting the use of intermittent flushing of cannulas (4). When a PIV is used for intermittent administration, it can be capped with a needleless connection, so-called intravenous lock (IVL).

Although IVLs are commonly used, the incidence of complications with non-elective removal as a result, is relatively high. Eighty percent of removals are due to complications such as obstruction, leakage, phlebitis, or extravasation (5). The majority of IVLs last for 15 to 54 hours resulting in a high rate of new insertion attempts, which may potentially be harmful (6). As a result of these insertion problems, there is often a discontinuation of vascular access, which may result in deficits in TPN (7).

Heparin solution is frequently used as a regular flush solution in our NICU to prevent clotting of the IVL. However, heparin is incompatible with many types of medication. Heparin administration has also been associated with severe complications. Overdosage due to wrongly prepared solutions can be dangerous. Young described a tragedy in which several premature babies died because of a 1,000-fold overdose of heparin (8).

One of the core topics of the Dutch patient safety systems in NICUs is the safe preparation and administration of high-risk medication in children. The necessity and the safety of the use of heparin in this patient group are questionable.

The use of saline as a standard flush solution as an alternative for heparin has become common practice in adults (9,10). However, adults and neonates differ in many aspects. The application of results from adults to children without a separate analysis of the effects in neonates should be discouraged.

Therefore, future studies that provide a better insight into the prevention of complications and that may result in recommendations to promote longevity of IV catheters, are important for this critically ill group of newborn infants.

2. Central Venous Catheter

A central venous catheter (CVC) can be inserted in those situations where medication or fluids with aberrant osmotic or pH values are necessary or where a peripheral IV catheter has failed, or where rapid IV medication directly after birth is needed. The most commonly used CVCs in the NICU are umbilical venous catheters (UVCs), peripherally inserted central catheters (PICCs) and surgically inserted central catheters (SVCs).

2.1 Umbilical Venous Catheter

Umbilical venous catheters (UVCs) are usually inserted on the first day post-partum. An UVC provides reliable vascular access for the administration of medication and TPN. The UVC in our NICU is inserted under aseptic conditions by neonatologists, nurse practitioners and residents. All of them follow a standard protocol outlining insertion practices (11). The tip of the UVC is positioned in the Inferior Caval Vein before the junction with the right atrium, at the level of the diaphragm. The catheter is attached with a suture through the umbilical jelly. A second attachment with plaster on the abdominal wall using a neo-bridge construction is usually made for additional safety (12). An X-ray is necessary to confirm the correct position of the catheter tip. The insertion site is disinfected with a 0.5% chlorhexidine/alcohol 70% solution twice daily. The risk of complications is directly related to UVC longevity (13,14). The protocol therefore prescribes removal of an UVC as soon as possible or by day 7. However, sometimes an UVC remains in situ longer than 7 days due to the difficulties to place a PICC in newborns with severe illness. Other reasons to remove an UVC are the end of therapy or the presence of complications. Because of the possibility of excessive blood loss, obstruction and leakage, a newborn with an indwelling UVC is mostly positioned laterally or supine in our NICU, to facilitate observation of the umbilical region. However, the prone position has been advantageous for preterm newborns with respiratory distress (15,16). Prone position is relatively safe until the 32nd week gestational age as long as the heart rate and breathing are monitored (17). Therefore, it presents a practical dilemma for preterm newborns with respiratory distress and an indwelling UVC, whether prone position may increase the complication rate of UVCs.

2.2 Peripherally Inserted Central Catheters

A peripherally inserted central catheter **(**PICC) is usually inserted when long-term IV medication or TPN is necessary after removal of the UVC, or when UVC insertion has failed. A PICC is inserted in one of the major peripheral veins (i.e. basilic vein, cephalic vein, greater saphenous vein, or temporal vein). The most common insertion technique used in NICUs is the catheter-through-needle technique (18). An alternative technique is the catheter-over-guide wire technique, which is a modification of the technique described by Seldinger (19). This technique is the method of choice in our NICU because of advantages such as allowing entry into difficult-to-access veins, a greater success rate in placing a PICC and a higher percentage of central positioning of the catheter tip (20,21). In our NICU, a team of well-trained neonatologists is responsible for inserting a PICC on the ward under maximum aseptic conditions. A PICC is often inserted after the second postnatal day. However, this may result in an increased risk for nosocomial infection when compared to UVCs because the newborn has already been colonized with hospital-acquired micro-organisms (13).

Within the framework of patient safety it is desirable to compare the CLABSI incidence between both types of CVCs in newborn infants.

2.3 Surgically Inserted Central Catheters

A surgically inserted central venous catheter (SVC) is placed by a dedicated team of well-trained paediatric surgeons in the subclavian vein via percutaneous insertion, or in the jugular vein through a cut-down method. Placement of an SVC is indicated when insertion of an UVC or PICC fails. The SVC is usually inserted in the operating room. We excluded analysis of this catheter in our studies because of the small numbers of this procedure.

Standard care of CVC

After insertion, all central venous catheter tip positions are verified by an X-ray and, when necessary, repositioned.

Administration of medication or TPN with the exception of blood products can be started when a correct position is reached. Administration of blood products is not recommended because of the small lumen of the CVC, which can be easily obstructed. Aspiration of blood is minimized because of the obstruction risks.

Heparin is continuously administered at a dose of 2 units per hour in order to reduce the risk of thrombus formation (22). Sha and Sha concluded in their Cochrane review that administration of heparin increased the longevity of central venous catheters (23).

The entire drip system of the UVC is replaced every 96 hours in accordance with hospital protocol. Drip systems for administration of intralipid (fat solution) are changed every 24 hours. The catheter insertion site is checked every 2-4 hours. All nurses in the NICU are trained in the care for a CVC and recognition of signs of complications. Every 3 years they complete a refresher-training course.

Neonatologists are trained during their fellowship in insertion of UVCs and PICCs and recognition of complications. Residents are trained in insertion of an umbilical catheter during their internship in the NICU.

Complications

Unfortunately, IV access devices are not only associated with minor, but sometimes with severe complications. These complications can be divided between insertion complications and complications during the indwelling time of a CVC. The most important CVC related complications during indwelling time are CLABSI (complication

range 2.3-22.0 CLABSI per 1,000 catheter days), thrombosis (complication range 13.0% to 30.0%), catheter leaks or damage (complication range 0.0%-5.9%), and occlusion (complication range 2.2% to 33.6%) (24,25,26,27,28,29).

Although all complications of CVCs are monitored, most attention in the NICU goes to CLABSI (30,31,32). CLABSI was previously thought to be an unavoidable complication of hospital care. These complications lead to high hospital costs (i.e. in the United States between $ 36 and $ 45 billion per year). However, during the last 5 years health care associated infections such as CLABSI are now considered to be avoidable. A large number of studies have been performed showing that CLABSI can decrease by using bundles (32,33). However, none of these studies describe whether there may be an influence on CLABSI when taking care of a newborn with an umbilical catheter in prone position. Also most of the studies with PICCs have been done with a catheter inserted using the catheter-through-needle technique. We could not find studies describing the effect of bundles on catheters inserted using the modified Seldinger technique. Also studies were not available regarding the use of the Seldinger technique as insertion technique and its influence on CLABSI.

Aims and outline of the thesis

The overall aim of this thesis is to improve the quality of nursing and medical care in newborn infants with venous access devices, and to raise the awareness of the potential complications of these catheters. Our principal goal was to increase patient safety and quality of care. We started with the analysis of the most frequently used technique with the lowest number of major complications, the peripheral IV catheter and ended with specific nursing care and insertion techniques in central venous catheters.

It is important to select the best possible option for IV access in the newborn in order to achieve the treatment with the lowest complication risk. The risks and benefits of the different catheters must therefore be carefully balanced, given the risk of catheter related complications and the necessity to increase patient safety.

Our studies are reported in 5 chapters. Following the introduction (*Chapter 1*), we presented data from a study on the most frequently used venous access device: the peripheral IV catheter (PIV). In this study we analysed only PIVs used for intermittent administration, so-called intravenous lock (IVLs).

A prolonged indwelling time of an IVL is an important goal. Heparin was administered to prevent obstruction and to prolong the indwelling time of the catheter. However, the use of heparin to prevent clotting, thus obstruction of an IVL, is not without risks in this vulnerable patient population. In adults, the use of saline as flush solution for IVLs has

been a common practice for many years. To avoid unnecessary use of heparin we initiated a double blind randomized trial comparing the effect of heparin versus saline in IVLs. The indwelling time and complications were analysed in both groups *(Chapter 2*).

In *Chapter 3* we retrospectively analysed the complication incidence in the 2 most common forms of central venous catheters, the umbilical venous catheter (UVC) versus the peripherally inserted central catheter (PICC) using the modified Seldinger technique and provided recommendations on nursing and medical care.

In *Chapter 4* we prospectively analysed the complication rate of newborn infants with an indwelling UVC in prone position because this position supposedly has respiratory advantages. Previously, prone position with an indwelling umbilical catheter was assumed to be associated with an increased percentage of catheter complications. We could not however, find any evidence to support this assumption in the literature and therefore performed this study.

In *Chapter 5* we described whether specific preventive bundles in PICCs using the modified Seldinger insertion technique, reduced the central line associated blood-stream infection (CLABSI) incidence. The modified Seldinger technique provides a more central position of the catheter tip but this insertion requires multiple steps when compared to the traditional technique and may influence the CLABSI incidence.

In *Chapter 6* we presented preliminary data regarding the use of preventive bundles to decrease CLABSI in newborn infants with an UVC.

The most important findings of this thesis are summarized in *Chapter 7*. Conclusions are presented with suggestions for future research.

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Effectiveness of heparin solution versus normal saline in maintaining patency of intravenous locks in neonates: a double blind randomized controlled study.

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Abstract

Aim: The aim of this study was to evaluate the effect of heparin versus saline as flush solution for maintaining patency in peripheral intravenous locks in neonates and to investigate whether other variables influence the longevity of intravenous locks.

Background: Heparin is usually used as a regular flush solution to prevent occlusion of peripheral intravenous locks in neonates. There is no clear recommendation using heparin or saline flushing peripheral intravenous locks in neonates. The disadvantage of heparin cannot be ignored, especially in this patient group.

Methods: In a double blind prospective randomized study, neonates (gestational age >27 weeks) with intravenous locks were randomly assigned to receive heparin or saline as a flush solution in a 21-month period (2002-2004). The main outcome was the duration of patency.

Results: Eighty-eight neonates were included. No significant difference was found in patency of peripheral intravenous locks flushed with 0.7 ml heparin (10 units/ml) (n=42, median 56 h) or 0.7 ml saline (n=46, median 61 h). When the analysis was confined to remove locks due to non-elective events, no significant difference was found in duration of patency (p=0.27).

Conclusion: As no difference in patency could be established, using saline as a flush solution is preferable to heparin in peripheral intravenous locks in neonates, given the greater likelihood of complications associated with heparin. Although these data are more than 5 years old, the relevance of the outcome is still important for the clinical practice because of the potential adverse effects.

Introduction

On a Neonatal Intensive Care Unit (NICU) most of the patients receive continuous intravenous therapy in the first weeks after birth. Interruption of continuous intravenous medication (for example inotropics, sedatives, and anaesthetics) for the administration of intermittent medication is undesirable in severely ill neonates in the NICU. To avoid this interruption, the administration of intermittent medication and/or blood products is performed using an additional intravenous catheter or peripheral intravenous lock (peripheral IVL). This is an intravenous cannula capped with a needleless connection. Such a peripheral IVL should remain patent for as long as possible because insertion of a peripheral IVL is a painful procedure for the neonate. Moreover, the limited number of useful veins for cannula insertion in this patient group makes prolonged patency of the cannula an important issue. Therefore, administration of intermittent heparin solution is usually used as a regular flush solution to prevent occlusion of the peripheral IVL by clots. Based on available evidence, the use of saline as flush solution for peripheral IVLs instead of heparin has become common practice in adult and adolescent patients (1,2). However, this may not be the best option for neonates, since adults and adolescents differ greatly from the neonate in many ways. The intravenous cannula used in neonates is smaller than those used in adults and thus can be more easily obstructed. The issue, whether heparin should be used or not in this patient group, is clinically important, since the use of heparin is not without risk. Heparin can be associated with the occurrence of intraventricular haemorrhage (IVH) and heparin induced thrombocytopenia (HIT) in neonates (3,4,5,6,7). In particular premature infants have an increased risk of cerebral haemorrhage in the first few days of life (8).

In addition, heparin is incompatible with many types of medication, making it necessary to flush the peripheral IVL with extra saline prior to use, which gives a risk of fluid overload. A tragedy where several premature babies died after administration of a 1,000-fold overdose heparin, demonstrated the risk of heparin as a common medicine in maintaining catheter's patency (9). The management of a peripheral IVL in neonates depends on individual knowledge and practice. This varies between hospitals. There are no clinical practice standards for using a flush solution for peripheral IVLs in neonates.

During recent decades more studies have analysed the patency of a peripheral IVL flushed with heparin versus saline in neonates and children. Results of these studies, analysing a peripheral IVL patency flushed with heparin versus saline in only neonates are conflicting. Several studies showed no differences between heparin (with concentrations of 1-10 units/ml) versus saline on the longevity of a peripheral IVL (10,11,12,13,14). Other studies suggested that heparin solution is more effective in

maintaining patency than saline (15,16). Several studies used different brands and/or size of catheters. In Table 1, the heparin concentration, catheter diameter, sample size and outcome were shown. Some studies included data obtained from more catheters in the same patient, which could affect the outcome because differences in clinical conditions and the use of sedation are a potential bias in the results. Danek et al. (1992) showed a 12 hour prolonged longevity of heparin flushed peripheral IVLs in a 22 Gauge cannula versus a 24 Gauge cannula (17). It might be reasonable to assume that it will take longer for catheters with larger lumen to be obstructed by clot formation than a catheter with a smaller lumen. Therefore, it is possible that a catheter with a smaller lumen will have more benefit from heparin in the prevention of clot formation in order to keep its lumen longer patent. However, the 2 studies mentioned in Table 1, which has shown the benefit of heparin, have also been performed with a small lumen catheter (24-Gauge).

A meta-analysis, included 10 randomized or quasi randomized controlled trials (Shah et al. 2005) and a review (Trautmann et al. 2006) concluded that a recommendation for heparin use in neonates with peripheral intravenous catheters could not be made due to clinical heterogeneity and heterogeneity in outcome parameters (18,19). They concluded a lack of blinding in interventions and allocation. The dose of heparin and the administration method also varied widely. The frequency of flushing the peripheral IVL was not always mentioned. In these studies we could not find a clear recommendation for flush solutions giving a prolonged patency of a peripheral IVL. A trial with sufficient power and well-defined criteria is recommended.

Materials and methods

Study design

In view of the absence of clear recommendation in studies on the use of heparin or saline for flushing peripheral IVLs in neonates, we performed a prospective randomized study comparing heparin and saline. The primary aim of this study is to evaluate the effect of heparin versus saline as flush solution for maintaining patency in peripheral IVLs in neonates. The secondary aim of this study is to investigate whether other variables such as birth weight, age, location of peripheral IVL, primary or secondary IVL and medication have an impact on the longevity of peripheral IVLs. Our null-hypothesis is that there will be no difference in the patency duration between peripheral IVLs flushed with heparin and IVLs flushed with saline.

We performed a prospective randomized double blind clinical trial, using heparin versus saline in peripheral IVLs in neonates with a minimum gestational age of 27 weeks. The setting was a third level 15-bed NICU with an average of 400 admissions

Table 1 Overview of neonatal studies comparing the patency duration between intravenous locks flushed with saline and heparin

Author	Year	No IVL saline	No IVL heparin	Heparin concentration	Catheter diameter (Gauge)	Results in patency duration
Kotter	1996	75	43	10 units/ml	24	ns p=0.34
Paisley et al.	1997	54	33	10 units/ml	24	ns
Heilskov et al.	1998	27	28 35	2 units/ml 10 units/ml	24	ns p=0.88
Hanrahan et al.	2000	112	118	10 units/ml	Not mentioned	ns p=0.02
Mok et al.	2007	37	40 39	1 unit/ml 10 units/ml	22 (5.7%) 24 (94.3%)	ns p=0.72
Mudge et al.	1998	78	56	10 units/ml	24	Heparin longer patency p=0.02
Schultz et al.	2002	29	20	2 units/ml	24	Heparin longer patency p=0.04

per year. Neonates were randomized into 2 groups. Peripheral IVLs were flushed with 0.7 ml normal saline in the saline group. In the heparin group, peripheral IVLs were flushed with 0.7 ml heparin solution 10 units/ml. The 2 types of flushing solution were prepared daily by one of the clinical care coordinators of the neonatal medium care unit, who were not involved with the bedside care of the neonatal intensive care patients.

Randomization was obtained by opening a sealed, opaque envelope with a coloured card (red or blue) from a box in which the order of the envelopes was randomly determined before the start of the study. The colour referred to the type of flushing solution (red for saline, blue for heparin) that was used for the peripheral IVL for the individual neonate to ensure masking of the flush intervention and data analysis by the nurses.

Sample

A random sample of patients was recruited by the neonatal intensive care nurses who received instruction from the 2 investigators (I.J.J.A. and J.A.H.). All nurses were

individually instructed on study design and purpose, determining in- and exclusion sample criteria and randomization design. Neonates with a gestational age > 27 weeks were included and randomized in this study after informed consent. Each participating neonate was included for only one peripheral IVL in a 21-month period (September 2002- April 2004). Excluded from this study were neonates who were treated with Extra Corporeal Membrane Oxygenation (ECMO) and who received anti-coagulation treatment. The length of patency started when a new peripheral IVL was inserted or an intravenous cannula used for continuous infusion became an IVL. It ended when the IVL was removed, continuous infusion needed to start or the patient died.

Based on the mean duration of patency of 69 h (SD 32 h) in 17 peripheral IVLs in our NICU and assuming, as described in the study of Klenner et al. (2003), that a longevity difference with a minimum of 24 h between heparin and saline flushed peripheral IVL is clinically relevant**,** a calculation with a power of 90% indicated a minimal sample size of 40 peripheral IVLs in each group.

Data Collection

All 60 NICU nurses were competent in flushing peripheral IVLs. In their primary training as NICU nurses they are trained and assessed in the care of a peripheral IVL in neonates. All nurses will be assessed every 3 years about their competency in the care of a peripheral IVL. All these nurses were individually verbally instructed by the investigators on IVL patency, criteria for peripheral IVL removal and registration of the required data on data-sheets. The peripheral IVL solutions were labelled with a blue or red coloured sticker, which referred to the randomized colour of the peripheral IVL to ensure masking of the intervention. The nurses were unaware of the content of these bottles because the solutions were prepared daily by clinical care coordinators of the other ward (the neonatal medium care unit).

Observations

The following data of the required number of patients in each group were collected by the instructed nurses: gestational age, birth weight, postnatal age at the start of the trial, body weight at the start of the trial, primary diagnosis, presence of central venous and arterial catheters (both were continuously flushed with 2 units heparin/h regardless of the infusion rate), medication during the trial and peripheral IVL location. The duration of patency was calculated in hours from the moment the cannula was inserted (primary peripheral IVL), or an already present peripheral infusion became a peripheral IVL (secondary peripheral IVL), until the nurse decided that it needed to be removed. Inspection of the insertion area was carried out with a minimum of 6-times a day.

The peripheral IVL was removed in case of IVL failure (non-elective reasons), such as infiltration of the area (fluid infiltration, oedema), phlebitis (inflammation of the

vein with pain), obstruction of the cannula (difficult or impossible to flush, inability to administer fluid in 3 seconds), or fluid leakage (around the cannula-insertion). The peripheral IVL was also removed due to elective reasons for removal such as treatment was considered no longer necessary, dislocation due to movements, when the peripheral IVL had become a continuous IV infusion, discharge or death.

Materials and techniques

The peripheral IVL consisted of a 24-gauge intravenous cannula (Neoflon, 0.7 mm x 19 mm**,** Becton Dickinson, Helsingborg, Sweden) capped with a needleless connection (Smart Site, Alaris Medical Systems INC, San Diego, USA). On our NICU only this 24-gauge catheter was used for all neonates.

Peripheral IVLs were flushed at a minimum of every 8 hours, where possible adapted to medication administration. Using a peripheral IVL for administration of intermittent IV medication more than every 8 hours, the peripheral IVL must always be locked, using 0.7 ml of the solution in accordance with randomization. So in this study there is no limitation in the maximum amount of flushes given.

The flushing amount (0.7 ml) is determined by the volume of the total peripheral IVL system, included catheter, infusion line, needleless adapter and a little amount extra volume to ensure a total flush of the peripheral IVL system. As flush procedure, all nurses used the same method. This contained disinfection of the needleless adapter, flushing the 0.7 ml solution (using a 2 ml syringe) over 3 seconds, removing the syringe while maintaining continuous pressure and ending with disinfection of the needleless adapter. Five nurses, who are members of the NICU infusion team, received extra training for assessment about the necessity of peripheral IVL removal and for resolving any problems with data collection on the ward.

When there was uncertainty about the patency of the peripheral IVL, a second option was sought from one of the nurses of the infusion team. This nurse assessed the patency of the peripheral IVL and determined the necessity for the removal of the cannula. The second assessment reduced some of the potential bias.

Ethical considerations

The study was approved by the University Medical Centre Ethics Committee with the restriction to follow only 1 period of a peripheral IVL, starting when an IV cannula became a peripheral IVL until this had to be removed. Informed consent from the parents was obtained after verbal and written information of the purpose and design of the study by the investigators or instructed nurses in the first 24 hours post partum when a peripheral IVL was expected to be required in the near future.

This included the explanation of the participation of 1 peripheral IVL period, nursing controls, reasons for peripheral IVL removal, and advantages and disadvantages of the 2 flush solutions. After this verbal explanation, parents were given a 24-hour

period to consider the participation of their child in this study. At any time, the investigators or the instructed nurse were able to answer the questions. After written informed parental consent, neonates were randomized. Parents were allowed to terminate their participation at any time without giving any reason. The data of this study will be stored confidentially. Only the investigators have access on the original data.

Data analysis

Data were analysed using SPSS version 16. The analysis was performed with Kaplan-Meier survival analysis because this estimates the survival function of (life) time data; in this study the patency of a peripheral IVL. An advantage of this analysis is that the method takes the censored data into account. For all survival analysis, non-elective reasons for removal (infiltration of the area, phlebitis, obstruction of the cannula, fluid leakage) are considered as a failure of the peripheral IVL.

The elective reasons of removal (end of therapy, dislocation, when the peripheral IVL had become a continuous IV infusion, discharge or death) are treated as censored. The log rank test was used to assess statistical significance. To be able to correct for possible confounders on the relation between survival and group (heparin or saline) Cox regression analysis was used and hazard ratios from the model were presented with 95% confidence interval (CI). Relations in cross tabs were tested using the chi-square test.

Results

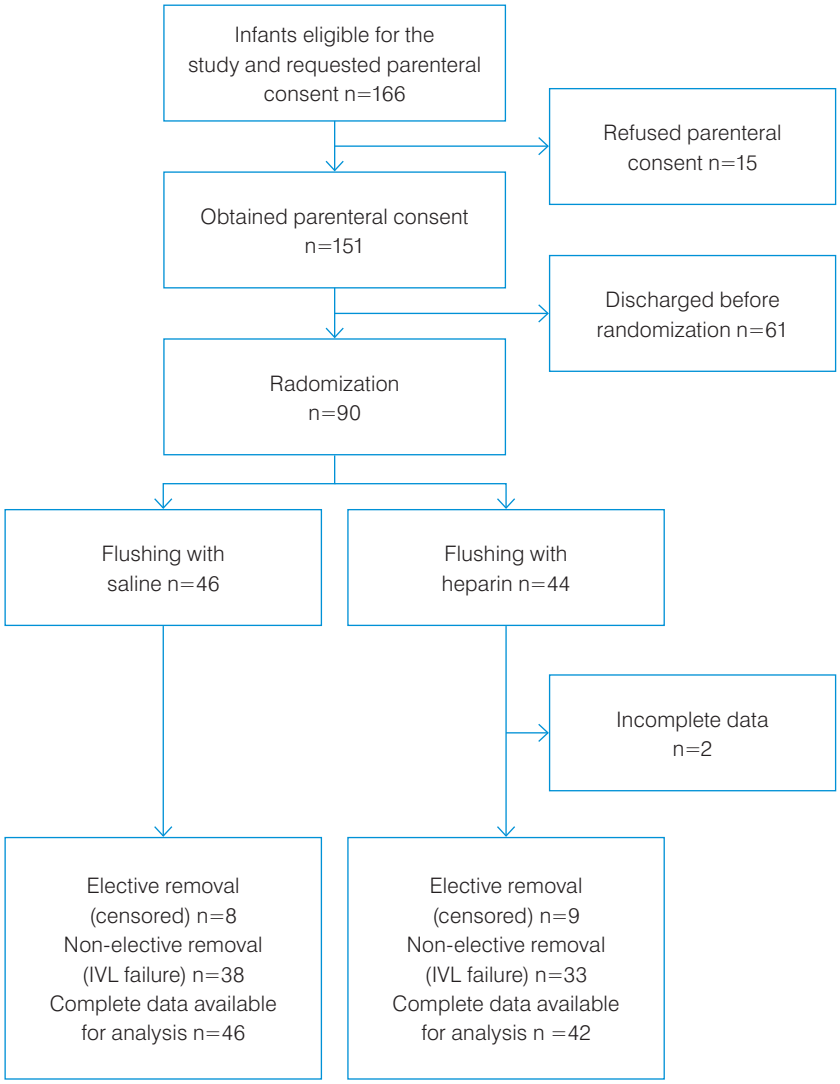
A total of 166 parents were approached for their consent to participate in the trial. Finally, 88 peripheral IVLs were used for analysis (Figure 1): 42 received the blue coded solution (heparin) and 46 received the red coded solution (saline).

The groups were similar at baseline with respect to gestational age, birth weight, gender, postnatal age, body weight at the start of the study, percentage of primary peripheral IVLs, presence of heparinised arterial or central venous catheters and primary diagnoses as shown in table 2.

In 17 cases (8 saline and 9 heparin) there were elective reasons for removal of the peripheral IVL, which was considered as non-failure of the IVL (Table 3).

The peripheral IVLs in the heparin group had a median patency duration of 56 hours. The peripheral IVLs of the saline group had a median patency of 61 hours. Median patency duration was established using Kaplan-Meier survival analysis. The Kaplan-Meier plot shows similar proportions of IVLs remaining patent in the saline and heparin groups at times up to 400 hours (Figure 2); the slightly lower percentage of

Figure 1 Flow chart



patent IVLs between 50 and 150 hours in the saline group was not statistically significant (log rank test p=0.27). In this study there is a slight imbalance in the use of medication between the heparin and saline group (Table 4).

Table 2 Characteristics of study population

	Saline n=46	Heparin n=42
Male: Female	30 : 16	23 : 19
Gestational age *at birth* (weeks)	32.0 (26.0-41.3)	32.1 (25.6-41.5)
Birth weight (g)	1804 (600-4000)	1726 (471-4015)
Gestational age *at randomization* (weeks)	34.2 (27.4-44.0)	34.0 (27.1-43.2)
Body weight *at randomization* (g)	1905 (710-4000)	1824 (592-4244)
Primary peripheral IV (%)	37 (80.4)	37 (88.1)
Presence of heparinised arterial catheter (%)	11 (23.9)	14 (33.3)
Presence of heparinised central venous catheter (%)	17 (36.9)	22 (52.4)
Prematurity (%)	11 (23.9)	7 (16.7)
Prematurity and respiratory distress (%)	17 (36.9)	23 (54.8)
Meconium Aspiration Syndrome (%)	2 (4.3)	2 (4.8)
Congenital Diaphragmatic Hernia (%)	4 (8.7)	4 (9.5)
Congenital heart defect (%)	5 (10.9)	3 (7.1)
Other respiratory distress (%)	0 (0.0%)	1 (2.4)
Other diseases (%)	7 (15.2)	2 (4.8)

Values are mean (min-max) or otherwise as mentioned

When group allocation was considered in a Cox regression uncontrolled for any other factors, the risk of IVL failure was slightly though not significantly greater in the saline compared to the heparin group (hazard ratio saline versus heparin: 1.3; 95% CI: 0.81 -2.10, p=0.27). Correcting this result for all possible confounding variables like heparinised central venous and arterial catheters, location of peripheral IVL (upper or lower limbs), medication, primary or secondary IVL, gestational age and birth weight, still no statistical differences between the groups was found with the hazard ratio in the saline group reduced to 1.15 (CI: 0.70-1.90 p=0.51).

Only sodium bicarbonate had a possible relation on the patency of the peripheral IVL (Hazard ratio sodium bicarbonate using versus no sodium bicarbonate using: 0.65; 95% CI: 0.38 – 1.10, p=0.11). So in this study, administration of sodium bicarbonate in peripheral IVLs seemed to have a positive, but not a statistically significant effect on the survival of a peripheral IVL.

The heparin versus saline hazard ratio appears to be the same in both groups, irrespective of using sodium bicarbonate. The saline versus heparin hazard ratio was similar in the groups receiving sodium bicarbonate or not (p for interaction =0.80).

During this study, no haemorrhagic complications (such as IVH) were seen in either group.

Table 3 Reasons for removal

	Saline n=46	Heparin n=42	p-Value Chi-square
Non-elective reasons for removal	38 (82.6)	33 (78.6)	0.63
• Leakage	11 (23.9)	2 (4.8)	
• Phlebitis	4 (8.7)	6 (14.3)	
• Infiltration	9 (19.6)	9 (21.4)	
• Obstruction	14 (30.4)	16 (38.1)	
Elective reasons for removal	8 (17.3)	9 (21.4)	0.63
• Restart continuous • Infusion	1 (2.2)	4 (9.5)	
• Discharge	3 (6.5)	1 (2.4)	
• Death • Other	0 (0.0) 4 (8.7)	1 (2.4) 3 (7.1)	

Values are numbers (%) Other: end of treatment.

Table 4 Medications and blood products, administered through an intravenous lock during this study

Medication	Saline n=46	Heparin n=42
Blood products	16 (34.9)	24 (57.1)
Sodium Bicarbonate	10 (23.8)	19 (45.2)
Gentamicin	14 (30.4)	9 (21.4)
Phenobarbital	5 (10.8)	11 (26.2)
Furosemide	9 (19.6)	11 (26.2)
Amoxicillin-Clavulanic Acid	13 (28.3)	7 (16.7)
Amoxicillin	6 (13.0)	9 (21.4)
Ceftazidim	14 (30.4)	14 (33.3)
Erythromycin	3 (6.5)	2 (4.8)
Vancomycin	13 (28.3)	11 (26.2)
Flucloxacillin	3 (6.5)	2 (4.8)

Values are numbers (%).

Discussion

In neonates, flushing peripheral IVLs using heparin did not improve patency as compared to flushing peripheral IVLs with saline alone. Based on these results, we are not able to reject our hypothesis. In the absence of a clear advantage of flushing with heparin, we suggest that peripheral IVLs should be flushed using saline, since heparin may incur a greater risk of IVH (4,6) and HIT in neonates (3,5,6,7).

In our study, no IVH was observed. It should be noted, however, that our study was performed in that part of the postnatal period when the risk of IVH is reduced. Moreover, the daily dose of heparin administered in our study was much lower than the dose of 83.5 units heparin/kg/day, which has been shown to be related to increased incidence of IVH (20).

The incidence of HIT has not been investigated in our study. Two studies showed no evidence in induction of HIT antibodies using a low dose of heparin (0.5 –1.0 units/ml) in continuous infusion (20,21). However, 1 study found HIT in 14 out of 34 neonates with thrombocytopenia who received comparable heparin dose through an umbilical arterial catheter (3).

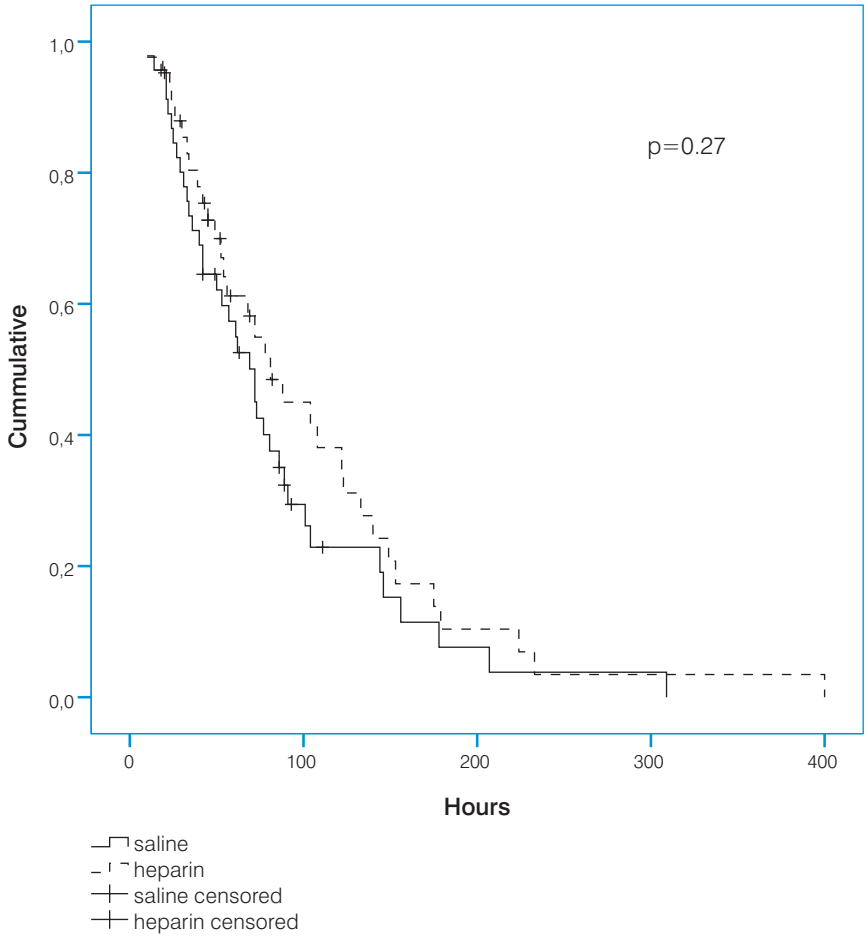
After discontinuation of heparin, thrombocyte count recovered in 75% of these infants. Further research would be necessary to assess whether HIT is a serious complication during heparin administration in neonates.

It can be expected that the presence of heparinised central venous and arterial catheters, location of peripheral IVL (upper or lower limbs), medication, primary of secondary IVL, gestational age and birth weight may have some influence on the outcome. Hanrahan et al. (2000) showed a significant effect of (birth) weight on the patency of a peripheral IVL (13). A peripheral IVL will easier cause infiltration in the smallest infants.

Using a Cox regression model we found no relationship between risk of IVL failure and the above-mentioned potential confounding variables between the heparin and saline group. Only sodium bicarbonate did prolong catheter patency, although we found no statistical significant difference or interaction between the heparin and saline groups. However, this finding is not surprising, as sodium bicarbonate has been used as flushing solution for catheter clearance when it is obstructed by precipitation of some (combination of) medications (22). Our peripheral IVLs have been used exactly for administration of intermittent medications and therefore it will increase the risk of precipitation in the peripheral IVL.

In this study we chose the option using the same material (24-Gauge cannula) in all patients because this was the commonly used material at that time on our NICU. Bias because of using cannula with different diameters which could influence the insertion procedure of the cannula, causing more or less vessel damage, was excluded. Probably using a 24-Gauge cannula can influence the longevity of a peripheral IVL

Figure 2 Kaplan- Meier survival analysis of patency of intravenous locks which had to be removed due to non-elective reasons for removal and censored for elective reasons for removal



between the very low birth weight population and the term born infants. Using a large cannula in the vulnerable small vessels of a very low birth weight newborn can probably cause more complications, which diminish the longevity of a peripheral IVL. Danek and Noris (1992) showed in a sequential assignment a significant difference in longevity using 24-Gauge catheters versus 22-Gauge catheters in neonates and children (17).

Using saline to flush peripheral IVLs in severely ill neonates will also have some economic benefits, since acquisition and preparation costs of heparin are not incurred and heparin-associated complications are avoided. In the study of Le Duc (1997), a cost saving of $ 9.45 per procedure has been estimated, which is based on an average of 8 procedures per 24 hour period, nursing time to prepare both solutions (heparin and saline), nursing salary and charge for the solutions (23).

A potential limitation of this study are the possible differences between nurses in the assessment of the necessity of peripheral IVL removal in case of imminent complication. Unfortunately, we didn't determine the interrater variability between nurses. A possible other weakness of the study could be the using of the same coloured label for the solution throughout the study. But the chance of a nurse finding out which coloured label referred to the solution is very low, because the solution was prepared daily on another unit by its own clinical care coordinators, not involved with the daily care on the NICU. Another point is the frequency of the flushes. We flushed a minimum of every 8 hours, 3 times a day. We did not analyse the effect of more flushes a day on the patency of an IVL. Finally, the assumptions used for the power analysis did not correspond to the results found in the final study. They were based on the pilot study, which gave an optimistic view of the dispersion in the data. As shown in the final study the dispersion was much larger than suggested by the pilot study. This indicates that a new study with a larger population with exclusively primary peripheral IVL might be necessary.

Conclusions

In conclusion, we were unable to demonstrate that heparin flushing of peripheral IVLs in neonates results in clinically important improved patency as compared with flushing using saline. This agrees with most results of other studies. In view of the possible adverse effects of heparin, we recommend normal saline as a flushing solution. Because of some limitations of this study we recommend a new study with a larger population using the same catheter size in peripheral IVLs.

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3

Comparison of complication rates between umbilical and peripherally inserted central venous catheters in newborns

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Abstract

Objective: The aim of this study was to compare the complication rates between umbilical venous catheters and peripherally inserted central catheters in newborns and to investigate whether other variables might increase the complication rate of the catheters.

Design: A retrospective observational study.

Setting: A level III neonatal intensive care unit.

Participants and Setting: Newborns (gestational age 24-42 weeks).

Methods: All central venous catheter-related complications were retrospectively analysed in newborns. The differences in survival rates between the 2 types of central venous catheters were evaluated using a Kaplan-Meier survival analysis with removal because of complications as the event of interest.

Results: In total, 140 umbilical venous catheters and 63 peripherally inserted central catheters were included. There were no significant differences in removals due to complications between the 2 catheters. The central-line associated bloodstream infections had the highest complication incidence, followed by obstruction, dislocation, leakage, and extravasation. There were no influences of gestational age, birth weight, and the use of subsequent catheters on the complication incidence.

Conclusion: A high complication incidence resulted in removal of the catheters, but it was not significantly different between the 2 catheters. The prevention of complications should be an important goal in the daily care of these patients.

Introduction

For more than 40 years, central venous catheters (CVCs) have been commonly used in neonatal intensive care units (NICUs) to administer fluids, medications and total parenteral nutrition (TPN) to critically ill newborns. The most commonly used CVCs in the NICU setting are umbilical venous catheters (UVC) and peripherally inserted central catheters (PICC). An UVC is inserted in the umbilical vein. This access can be used in the first 2 days after birth. After 2 days, the umbilical stump is usually dried, which makes insertion difficult. Moreover, after 2 days, the umbilical stump becomes colonized by micro-organisms, and therefore, the insertion of a UVC at this time is not recommended (1). Our protocol prescribes the removal of an UVC before or at day 7 when possible, because we assume an increased risk of central line associated bloodstream infections (CLABSI) related to longer UVC longevity as a result of this umbilical stump colonization. However, in practice, many UVCs frequently remain in longer than 7 days.

A PICC is inserted in one of the major peripheral veins. Insertion can occur in the first day after birth (when UVC insertion has failed) or at any point during the entire NICU stay. A PICC can be inserted after a UVC is (electively) removed or when a previous CVC is removed because of complications and continuous intravenous therapy or TPN is still necessary. Therefore, a PICC can be inserted as a second, third, or sometimes fourth subsequent CVC in a newborn. The elective removal of a PICC occurs only when treatment is no longer necessary. However, a CVC, whether it is an UVC or PICC, is not without risk. Complications, such as pleural effusion, obstruction, extra-vasation, thrombosis, leakage and CLABSI can occur (2,3,4,5,6). In the literature, the complications of 1 type of CVC or even just 1 complication primarily are analysed. This is understandable because a proper, balanced comparison cannot be made. Apart from the difference in the vascular access and postnatal age of the newborn when inserting a CVC, the sequential use of the CVC is another difference between the UVCs and PICCs. However, a comparison between the 2 types of CVCs, despite these differences, can improve our knowledge about the complication incidence, facilitating a more informed choice for using or continuing a CVC. Only then, improvements can be made to reduce morbidity, mortality and health care costs.

The primary aim of our study was to compare the complication incidence between UVCs and PICCs in our NICU. The secondary aim was to determine whether other variables such as birth weight, gestational age, and the use of subsequent CVCs increase the complication rate. The knowledge of the incidence of CVC-related complications is important in the care of vulnerable newborns. If this information is known, measures can be developed to reduce the complications of CVCs in NICUs, such as for example CLABSI. CLABSI reduction would result in decreased mortality and a reduction in health care costs (7).

Materials and methods

Sample

The study cohort was enrolled from a tertiary-level 17-bed NICU with an average of 500 admissions per year. Newborns were included if they 1) had a gestational age between 24 and 42 weeks and 2) had a CVC (UVC or PICC) inserted in our ward.

Newborns were excluded if their catheters were removed within 24 hours after insertion because it is expected that the complication rate would be very low in such a short in-situ duration. They also were excluded if they had a CVC inserted in another center because of possible differences in the insertion procedure that might affect the complication rate or had incomplete data. Lastly, newborns who underwent extra corporeal membrane oxygenation (ECMO) treatment were excluded because ECMO induces clotting activities that results in an increased risk for thrombi formation. Therefore, these newborns were treated with continuous heparinization to reduce the thrombi formation risk (8,9). Thrombi formation can also increase the risk of CLABSI (10).

Study design

In this retrospective observational study, clinical characteristics, catheter type, insertion site, complications, CVC longevity, and the reason for removal were collected by 2 investigators (IJJA & LMB) from the patient data management system and medical records for a 16-months (2005-2006) period. The investigators checked each other's work to increase reliability. CVCs were followed until their removal or when a newborn died or was transferred.

The reasons for CVC removal were grouped into elective (end of therapy, death, transfer to other hospital) and non-elective reasons. Non-elective reasons included obstruction of the CVC (i.e., difficulty or inability to flush the catheter or inability to administer fluid in 3 seconds), leakage from the CVC insertion site, CVC dislocation, pleural effusion/extravasation of fluid into the tissue, or CLABSI.

In this study, we used a CLABSI definition for patients $<$ 1 year old, based on the Centers for Disease and Control (CDC) definition (11). CLABSI was defined as a laboratory-confirmed bloodstream infection with an UVC or PICC in place for a minimum of 2 days and in place on the day of event or the day before. Laboratory- confirmed bloodstream infection was defined by using 1 of the first following definitions: Criterion 1 was defined as 1 or more positive blood cultures, with the exception of skin micro-organisms, not related to another infection source. Criterion 2 was defined as clinical signs of sepsis (especially for patients $<$ 1 year old), such as fever or hypothermia, apnea or bradycardia, and 2 or more positive blood cultures drawn on separate occasions with the same micro-organism (including skin micro-organisms) and no other infection source. The criterion had to be satisfied within a timeframe that did not exceed a gap of 1 day. However, this CDC definition may not cover all CLABSI in the

NICU, since it will only include laboratory-confirmed bloodstream infection. Additionally, the small blood volume which can be hardly obtained in newborns for blood culture, is frequently insufficient for sensitive detection of bacteremia (12). So in practice, clinical signs as apnea, hyper- or hypothermia and bradycardia are frequently the only first manifestations of sepsis in this vulnerable patient group with an indwelling CVC. This is usually sufficient enough to classify these cases as 'clinical sepsis' and to start treatment with antibiotics. However, many of them don't have a positive blood culture, probably due to above mentioned reason. Therefore, we defined 'clinical sepsis' as a derivative of the definition of van der Zwet et al. (2005) and Horan et al. (2008) belonging to Criterion 3: clinical signs of sepsis (see Criterion 2), but no or 1 positive blood culture (only skin micro-organisms), with no infection source other than a CVC (in situ or removed in 24 hours), and a medical reason to initiate sepsis treatment (11,13). In fact, criterion 3 is the same as criterion 2, but without positive blood culture or with just 1 positive blood culture with only skin micro-organisms. The overall CLABSI incidence was described as CLABSI that fulfilled any one of these 3 criteria. Because CLABSI criterion 3 is not included in many studies, we will discuss the CLABSI incidence related to criterion 3 apart from the CLABSI incidence related to criteria 1 and 2. After CVC removal, a tip culture was not routinely performed, except when the CVC was removed due to clinical signs of sepsis. A tip culture was followed by a blood culture when possible. Depending on the outcome of the cultures (and no other source for infection than the CVC) this was defined as a criterion 2 or 3 CLABSI. Ultrasound investigation was performed in cases of suspected thrombus formation.

Materials and techniques

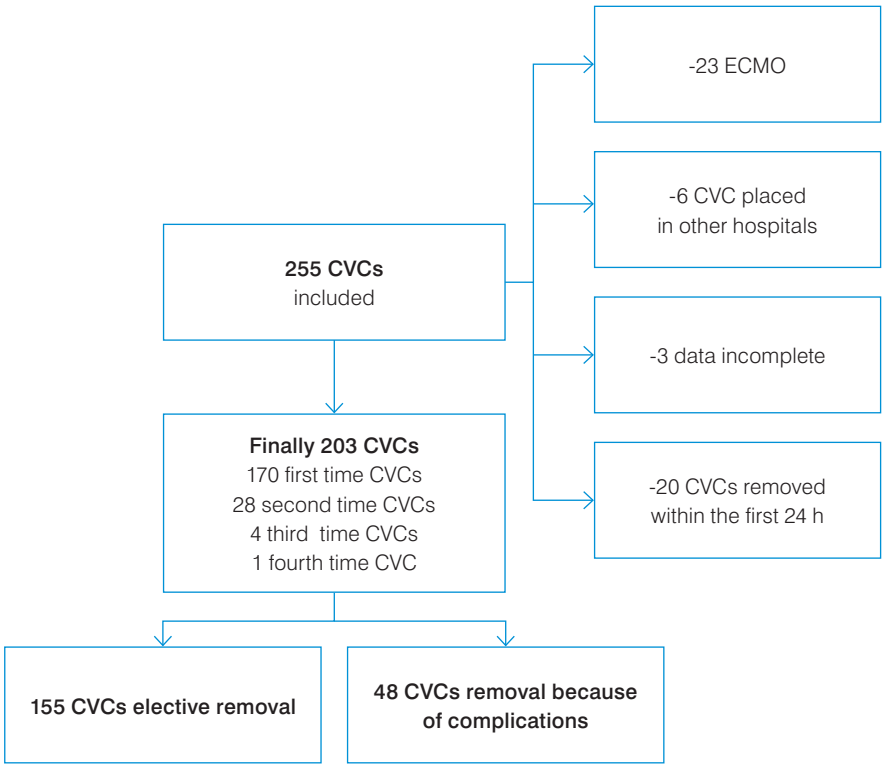
UVCs are typically inserted in the umbilical vein in the first 2 days post-partum. The UVC (Ch 5, Kendall Argyle, Tyco Healthcare, Tullamore, Ireland) is inserted under aseptic conditions by trained neonatologists, nurse practitioners, and resident physicians, all of whom follow a standardized protocol outlining the insertion practices. The tip of the UVC is positioned in the inferior vena cava just before the junction with the right atrium region, at the level of the diaphragm. The catheter is fixed with a suture through the umbilical jelly. A second fixation of the catheter with plaster on the abdominal wall using a neo-bridge construction is generally performed for additional safety (14). In our center, the insertion site (not the skin) was disinfected with a 0,5% chlorhexidine/alcohol 70% solution twice daily to conform to hospital policy. A PICC (Leaderflex, polyurethane catheter, 22 gauge, Vygon, Aachen, Germany) is usually inserted when long-term intravenous medication or TPN is necessary after removal of the UVC or when UVC insertion has failed. A PICC is inserted in one of the major peripheral veins (i.e., basilic vein, cephalic vein, greater saphenous vein, or temporal vein). In our center, the modified Seldinger technique is

the standard procedure for inserting a PICC. In the Seldinger method, a guidewire is used to achieve a central position in the junction between the superior vena cava and the right atrium or between the inferior vena cava and the right atrium (15). A team of trained neonatologists are responsible for inserting a PICC in the NICU under maximum aseptic conditions. After insertion, the catheter is covered at the insertion site by a sterile transparent film dressing (Tegaderm, 3M Health Care, St. Paul, MN, USA). This dressing is only changed when it becomes loose from the skin. After placement of the CVCs, the position of the tip is verified by X-ray and repositioned if necessary before TPN or drugs are administered. Heparin is continuously administered at a dose of 2 units per hour in both types of CVCs to prevent clotting. At the time of this study, all CVCs used were single lumen CVCs. The CVCs were not used for administration of blood products. Blood was not drawn from the CVC unless sepsis was suspected, and a CVC culture was necessary. NICU nurses replaced the entire drip system for all CVCs every 96 hours as a standard of care. The drip system for the administration of intralipid (fat solution) was replaced every 24 hours. The catheter insertion site was examined by trained NICU nurses every 2 hours for signs of inflammation or leakage as a standard of care.

Data Analysis

SPSS 20.0 for Windows was used for statistical analysis. The incidence of infection was measured as infection episodes per 1,000 catheter days. To assess the statistical significance of differences between categorical variables, Pearson's chi-square test was used or, when necessary, Fisher's exact test (in cases where one or more cells had an expected count of less than 5). The effects were considered statistically significant at a 0.05 threshold ($\alpha=0.05$). The mean and standard deviation were used to describe continuous variables that followed a normal distribution. The primary aim of this study was accomplished using a survival analysis. The differences in survival rates between the 2 types of CVC were evaluated using a Kaplan-Meier survival analysis to determine a predictor in which the event was defined as the removal of the CVC because of a complication. To correct for possible confounders, e.g., CVC longevity, gestational age, birth weight, and the use of subsequent CVCs, Cox regression analysis was used with the event defined in the same manner. In a Cox regression analysis, the association between a predictor and the occurrence of the event is presented as a hazard ratio and a 95% CI. A T-test was used to analyse whether birth weight, gestational age and duration of a CVC were significantly different between the UVC and PICC groups.

Figure 1 Flow chart of central venous catheter inclusion and removal



Results

In the 16-months study period, 255 CVCs were inserted in 232 newborns with a total catheter duration time of 1610 days. In total, 203 CVCs met the inclusion criteria and were used for analysis (Figure 1). In the PICC group, the mean birth weight and gestational age were significantly lower than in the UVC group (respectively $p=0.01$ and $p<0.00$). There was also a significant difference in the indwelling time between UVCs (6.9 days, min 2 days, max. 14 days) and PICCs (10.2 days, min 2 days, max 24 days, $p< 0.00$, Table 1). Despite our policy that states that a UVC has to be removed before, or at day 7 when possible, we determined that 49.7% of the UVCs remained in longer than 7 days (max 14 days). Although there was a significant difference in the duration between the PICC and UVC group, a conclusion could not be made because of the elective removal of UVCs at 14 days. Therefore, a Kaplan-Meier survival analysis for the first 14 CVC days was conducted.

Table 1 Characteristics of study neonates

	UVC n=140	PICC n=63	t-test p-value
Birth weight (grams)	1986 ±1118	1530 ± 937	$p < 0.01$
Gestational age (weeks)	33.2 ± 5.0	30.6 ± 4.4	$p < 0.00$
CVC indwelling time (days)	6.9 ± 2.7	10.2 ± 5.2	$p < 0,00$

Values are mean ± standard deviation
CVC = central venous catheter, UVC = umbilical venous catheter, PICC = peripherally inserted central catheter

Comparison of the complication incidence between the UVC and PICC groups

The majority of CVCs were electively removed because of termination of treatment/death or transfers (n=55, 75.9%, Table 2). The differences in survival rates, in the first 14 days because of the elective removals between the UVC group and PICC group, were determinded using a Kaplan-Meier survival analysis. This analysis examined the UVC and PICC survivals with complications (event) as the reason for removal. There was no significant difference in catheter removals between the UVCs and the PICCs in the first 14 days (log rank test p=0.66, Figure 2). In 23.6 % (n=48) a complication was the reason to remove a CVC. CLABSI was the most common complication. When using a survival analysis for a CVC indwelling time up to 14 days with CLABSI as an event, we observed no significant differences in removal because of CLABSI between the 2 types of CVCs (p=0.60, Figure 3). When CLABSI was defined as an overall CLABSI that fulfilled one of the 3 previously defined criteria, we found an incidence of 20 per 1,000 catheter days in all CVCs (16.3%, n=33). When CLABSI was defined in conformance with the CDC criteria (only fulfilling criterion 1 and 2), we found an incidence of 8 per 1,000 catheter days (6.4%, n=13). CLABSI meeting the criterion 3-definition (clinical sepsis) had the highest incidence at 12.4 per 1,000 catheter days (9.8%, n=20). *Coagulase-negative Staphylococcus* was the main cause for CLABSI in both groups (66.7%). In 66 (32.5%) cases, an ultrasound thrombus screening was performed. A thrombus was found in only 5 UVCs (3.5%) with an indwelling time longer than 7 days. No thrombi were found in PICCs and UVCs with an indwelling time < 7 days. Although the complication rate was low, the dislocation and leakage incidence was the highest in the UVC group. Extravasation or perforation occurred rarely. In PICCs only, 5 obstructions occurred with direct removal of the catheter as a result.

Table 2 Reasons for removing central venous catheter

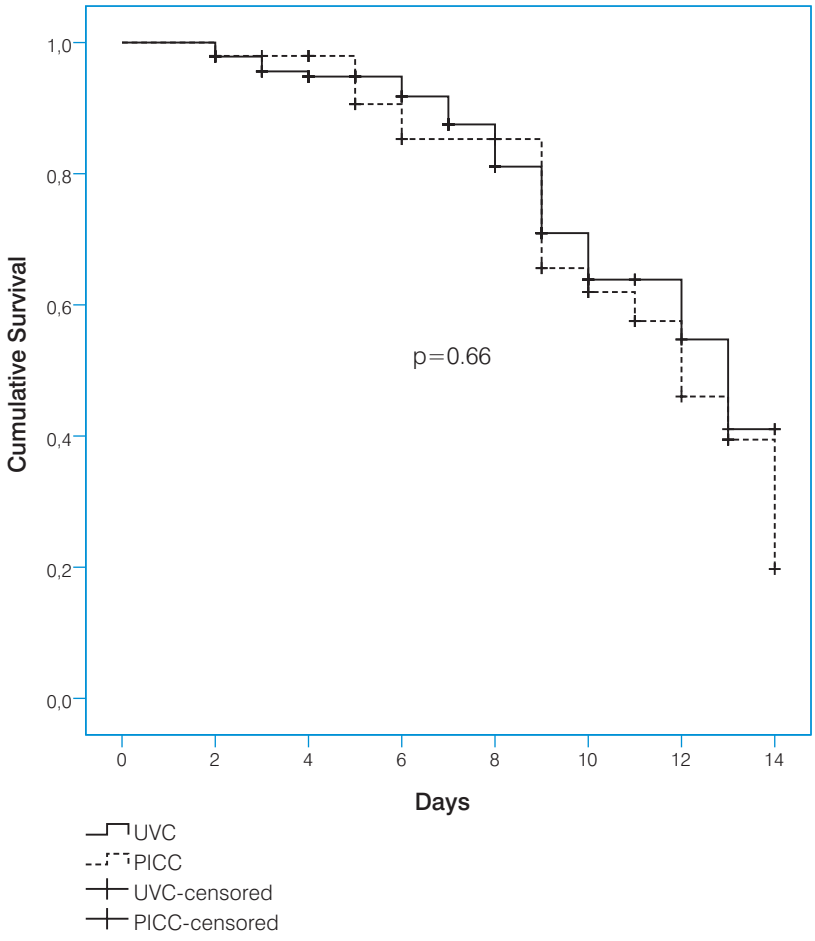
	Total n=203	UVC n=140	PICC n=63
End of treatment	103 (50.2)	79 (56.4)	24 (38.1)
Death/Transfer	52 (25.7)	33 (23.5)	19 (30.2)
CLABSI	33(16.3) 20.5 per 1,000 CVC days	21 (15.0)	12 (19.0)
CDC CLABSI (Criteria 1 and 2)	13 (6.4) 8 per 1,000 CVC days	6 (4.3)	7 (11.1)
Clinical Sepsis (Criterion 3)	20 (9.8) 12.4 per 1,000 CVC days	15 (10.7)	5 (7.9)
Obstruction	5 (2.5) 3.1 per 1,000 CVC days	0	5 (7.9)
Dislocation	4 (2.0) 2.5 per 1,000 CVC days	4 (2.9)	0
Leakage	4 (2.0) 2.5 per 1,000 CVC days	3 (2.1)	1 (1.6)
Extravasation/perforation	2 (1.0) 1.2 per 1,000 CVCdays	0	2 (3.2)

Values are numbers (%) unless otherwise mentioned
CVC = central venous catheter, UVC = umbilical venous catheter, PICC = peripherally inserted central catheter, CLABSI= central line associated bloodstream infection.
Total CVC days: 1610 days; UVC days: 979 days, PICC days: 631 days.

Possible variables that potentially influence the complication risks

Because of the significant differences in birth weight and gestational age between the CVCs, a Cox regression method was used to control for these variables. There was no influence on the complication incidence between the 2 CVCs when controlling for birth weight and gestational age (p=0.07 and p=0.2, respectively). There was a small incidence of a second (n=28), third (n=4), or fourth (n=1) CVC being inserted in the same patient. All UVCs were inserted as the first CVC with the exception of one UVC, which was inserted as a second CVC. The previous UVC was removed within the first few hours because of malposition of the catheter tip. A PICC was inserted as the first catheter in 30 newborns, then as the second, third and fourth catheter in respectively 27 newborns, 4 newborns, and 1 newborn. Most of the subsequent PICCs were inserted because an UVC was electively removed around day 7-14 (policy of our ward), and there was still a persistent need for TPN or intravenous medication. Out of all the UVCs (n=72) removed in the first 7 days, only 8 UVCs (11.1%) were removed because of CLABSI and were treated with antibiotics. Three of these UVCs were followed by a new insertion of a PICC within 24 hours of the removal

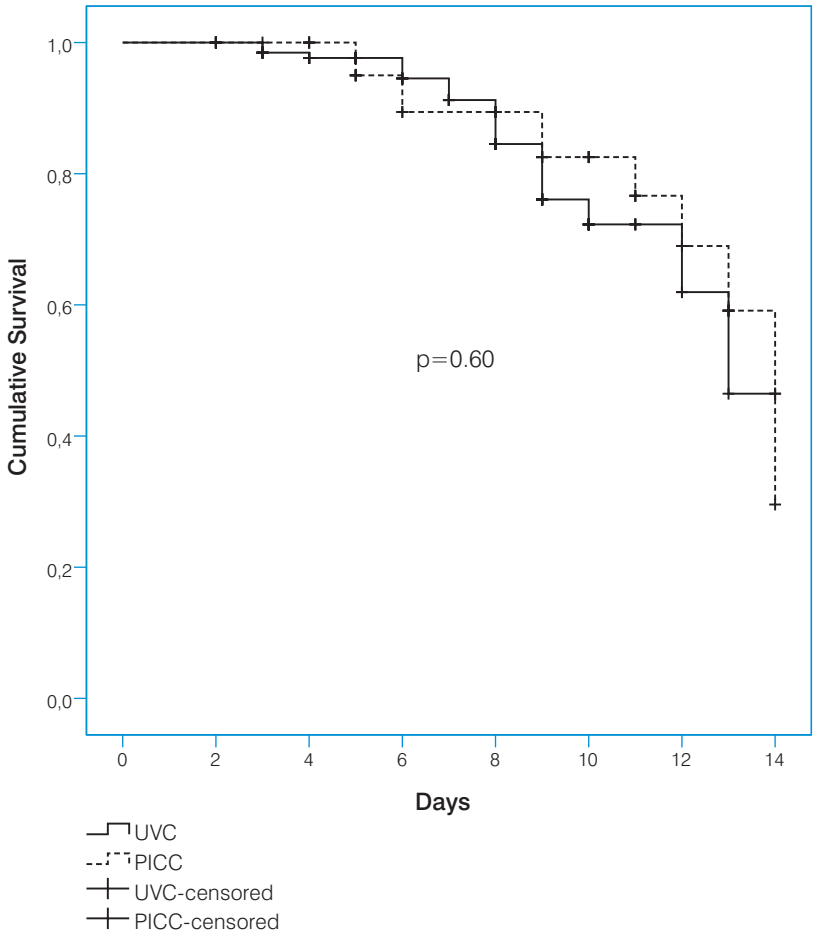
Figure 2 Kaplan-Meier survival analysis. Longevity of central venous catheters in the first 14 days with complications as reason for removal. Complication is the event



of the UVC. CLABSI was not observed in these subsequent PICCs that remained in situ for 6, 13 and 17 days.

When analysing the effect of the first CVC versus subsequent CVC on complications as a reason to remove a CVC, we used a Cox regression analysis with complications as an event. There was no difference in complication incidence between the first CVC group and the subsequent CVC group. The hazard ratio of the first CVC versus subsequent CVC was 0.48 (CI 0.18-1.23, p=0.13). Therefore, the use of a subsequent CVC did not affect the primary outcome of this study.

Figure 3 Kaplan-Meier survival analysis. Longevity of central venous catheters in the first 14 days with CLABSI as reason for removal. CLABSI is the event



Discussion

To our knowledge, this is one of the few reports that include an analysis of all complications in UVCs and PICCs in a 16-months period in a NICU.

Comparison of the complication incidence between the UVC and PICC groups

Although we suggested in our introduction that UVCs had to be removed because of a greater number of complications because of the increase colonization of micro-organisms of the umbilical stump (which is the reason for our ward policy to remove an UVC at day 7 when possible), we could not confirm this in our study. We did not find a significant difference between UVCs and PICCs in complications resulting in the removal of the CVC in the first 14 days. UVCs maintained until day 14 as compared with PICCs appear to be relatively safe, most likely indicating that the elective removal of UVCs after 7 days is unnecessary. These results correspond to the advisory report released by the Centers for Disease Control and Prevention (16). A study performed by Butler-O'Hara et al. (2006) indicated that there was no significant increase in infection rates and other complications with an UVC duration up to 28 days when compared to UVCs followed by an PICC (17).

Of all complications, CLABSI was the most common complication leading to removal of the CVC. The incidence of CLABSI in our study was high compared with other studies. The incidences mentioned in the literature vary from 2.1-17.0 per 1,000 catheter days or 6.0%-36.8% depending on the definitions of CLABSI (17,18,19, 20,21,22,23,24). In our study, when CLABSI was defined according to the CDC/ NHSN definition (fulfilling only criteria 1 and 2), our CLABSI incidence was lower (8.0 per 1,000 catheter days). A clear CLABSI comparison between the studies cannot be performed because of clinical heterogeneity and heterogeneity in the outcome parameters and definitions. The higher CLABSI incidence in PICCs (Table 2) can possibly be explained by the differences in the application between the CVCs such as the time of insertion and indwelling time of the catheter. There is an increased risk of nosocomial infection due to advanced colonization that has already occurred during a NICU stay once a PICC is placed when comparing to an UVC (1,18). An UVC is placed directly after birth when the colonization rate is low. Additionally, since a PICC has a longer indwelling time, an increased complication risk can be expected due to more nursing care interventions like manipulations of the catheter hub for connection with the drip system of TPN (25,26). In our study, we found overall a significant difference in the indwelling time between the UVCs and PICCs. However, comparing only to UVCs and PICCs with a maximum indwelling time of 14 days we did not find a significant difference in survival of the CVCs due removal because of complication between these 2 groups.

The high prevalence of antibiotic use in the first week after birth (because of possibility of maternal infection) could also potentially decrease the CLABSI incidence. Jardine, Inglis and Davies (2008) concluded that the use of prophylactic systemic antibiotics in newborns with a CVC reduces the rate of suspected or proven septicemia, but there is no difference in the mortality rate (27). Therefore, the routine use of prophylactic antibiotics in infants with CVC cannot currently be recommended. In some centers, CVCs are flushed with antibiotics prior to removal. This method is believed to reduce the number of bloodstream infections caused by catheter removal (28,29). However, reducing the incidence of CLABSI is an important issue. Many previous studies have reported that participation in a national surveillance has resulted in CLABSI reduction (20). Multifaceted interventions, such as team education, strict insertion procedures, hand hygiene protocols and daily review of catheter necessity with prompt removal of the CVC when no longer needed, all appear to reduce CLABSI incidence (22,30). The mere increasing of the responsibility and awareness of healthcare workers to prevent this complication should be an initial starting point.

The complication incidence of obstructions in PICCs is somewhat striking. This is likely dependent on the prolonged duration of CVC use in patients with prolonged use of TPN and medicines. In addition, the smaller lumen of the PICC can influence this outcome. When comparing this outcome to those in the literature, the incidence found in the present study is relatively low (5,17). We found a low complication incidence of dislocation, leakage and extravasation, which is accordance with other studies.

Although we did not perform systematic thrombus screening, the overall thrombus incidence appeared to be at least 3.0%. The thrombi were all found on the tips of UVCs with an indwelling time of more than 7 days. In the literature, a thrombus range of 13% to 30% in UVCs is described (17,31,32,33). Morag et al. (2006) concluded that there was a high incidence of portal vein thrombosis (73%) in children with a history of an UVC during the neonatal period (34). The discrepancy with the results of our study may have been caused by the systematic screening performed at fixed time points in the other studies. Most likely, our thrombosis incidence would increase if standard screening was performed at fixed time points. Nevertheless, we cannot conclude that the standard use of heparin, as in our study, may have affected the outcome because of the small study population and the limits of the thrombosis screening points used in this study. In a Cochrane review, Shah (2011) concluded that there were no significant differences in the risk of thrombosis, CLABSI, and intraventricular hemorrhage when using prophylactic heparin in PICCs. Prophylactic heparin use in PICCs only reduced occlusion rates (10).

Other variables, which may influence the outcome, outside the differences in insertion time and indwelling time between UVC and PICC, are the variables gestational ages, birth weight, and the use of subsequent CVCs. We observed significant difference

in gestational age and birth weight between the UVCs and PICCs. These variables did not influence the outcome of the CVCs and their complications. However, several studies indicate that very low birth weight newborns are significantly more prone to CLABSI complications (1,19). Although the numbers in our study are limited, the use of a subsequent CVC did not increase the incidence of complications. Therefore subsequent insertion of PICC after removal of a UVC or previous PICC can be performed without limitation.

Limitations

The most important limitation of this study is that it included a small population in one center, and it was retrospective in nature. Another limitation is the age of the data (7 years old), but we believe these data are still relevant to contemporary practice because the material of the catheters, the method of insertion and hygienic care are unchanged. To the best of our knowledge, UVCs and PICCs are still used in most NICUs in developed countries. In addition, the outcome of this study will add new perspectives for clinical practice because of the limited number of studies comparing UVCs and PICCs and the limited available data on the effects of subsequent CVCs on the primary outcome of complication incidence. The policy to only withdraw a blood sample from the CVC when there was a suspicion of CLABSI analysis or a catheter tip culture instead of using a standard analysis might be a limitation of this study in regards to recognizing all occurrences of CLABSI. However, we followed each newborn for clinical signs of sepsis until 24 hours after removal of a catheter. This, at the minimum, would indicate clinical sepsis and conform to criterion 3. Therefore, we do not believe we missed any CLABSIs.

The inter-rater reliability between the 2 investigators was not specifically evaluated. However, the double-checking of the data and outcomes should have helped to prevent misclassification.

We think that the impact of different health care professionals on the CLABSI outcome in PICCs is low because staff members only inserted these catheters. Only the time needed for success full insertion of the CVC can possibly affect the outcome. Time for insertion was not recorded in the medical records. UVCs were inserted by trained resident physicians. Nevertheless, this group changes regularly so their skills differs and might influence the outcome of CLABSI in the UVCs. The time needed for CVC insertion and other possible influences of the health care professionals on complications are important questions for further research.

We could not study the influence of multiple CVC insertions on the primary outcome. A larger study, using only the first UVC and first PICC would most likely be more reliable. However, the postnatal age of CVC insertion (UVC in the first 48 hours after birth, PICC during the NICU stay) is most likely one of the most important confounder in this study.

Despite these limitations, this study offers a good starting point for further research and development. Further research in a large population is required to obtain more specific details of the incidence of complications with these catheters. Our findings indicate that the UVC is relatively safe.

Conclusions

When comparing the survival of a PICC versus an UVC in the first 14 days, there was no significant difference in the reasons for removal. CLABSI was the most common complication. There was no significant difference in CVC removal because of only CLABSI in the first 14 days between the 2 types of CVCs. Nevertheless, we concluded that our overall CLABSI incidence is relatively high and needs to be reduced. Because of the high incidence, the prevention of this complication has a high priority. Other variabels as birth weight, gestational age and subsequent CVC insertion, did not influence the outcome. The prevention of central venous catheter complications must be an important goal in the daily care of neonates in the NICU. Further research to decrease the complications associated with CVCs is recommended.

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4

Umbilical catheters complications in newborns during prone position: A pilot study

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Abstract

Introduction: It is not known whether prone position of newborns with umbilical catheters increases the complication risk.

Purpose: Analysing complications of umbilical catheters in newborns during prone positioning. Analysing if local complications as a wet or red rim increases severe complications.
Subjects: newborns (> 24 weeks-42 weeks gestational age) with an umbilical catheter, inserted on our third level 17-bed neonatal care unit.

Design: A prospective observational pilot study (September 2009 - September 2010).

Methods: Each neonate was positioned for at least 12 hours in 48 consecutive hours in the prone position.

Results: Eighty-eight newborns were included. Central line associated bloodstream infection was the main reason for catheter removal due to complications. A wet or red umbilical rim did not increase the major complications. The relative risk for central line associated bloodstream infection in case of pus excretion was 3.3 as compared to clean umbilical stump ($p=0.02$). There were no complications as excessive blood loss or obstructions.

Conclusion: An umbilical catheter should not be considered as a contra-indication for prone positioning. In case of wet rim or pus excretion from the umbilical stump, removal of the catheter should be seriously considered.

Introduction

The placement of umbilical catheters (UCs) in Neonatal Intensive Care Units (NICUs) is a common procedure. In the first 2 days after birth, the umbilical vein and the umbilical arteries can be used for the insertion of venous and arterial catheters. An umbilical venous catheter (UVC) is required to administer fluids, medications and parenteral nutrition to critically ill newborns. An umbilical arterial catheter (UAC) is used in critically ill newborns when frequent blood sampling is necessary or when continuous blood pressure monitoring is required. The use of UCs is not without risks. Several complications (in a range of 2,5% - 20%) of UVCs have been described in the literature, such as central line associated bloodstream infection (CLABSI), thrombosis, dislocation and extravasation (1,2,3,4,5,6).

For UACs, complication rates are reported from 5.5% to 32%, including complications such as vascular spasm, ischemia, haemorrhage, CLABSI and thrombosis (7,8). Frequent observation of the position of the UC in the umbilical stump has been proposed as a measure to prevent catheter complications such as dislocation, which can result in leakage and blood loss. For these reasons, in our NICU, the prone positioning of a neonate with an UC is not allowed. We assume that prone positioning will increase the risk of local complications too, such as a persistent wet umbilical stump or red umbilical rim. This might be a risk factor for developing major complications, such as dislocation and CLABSI. However, this presents a dilemma because prone positioning is assumed to be the best position for these vulnerable patients with respiratory problems (9,10). In a questionnaire completed by 10 Dutch NICUs, prone positioning of a neonate with an UC is a common practice in 7 NICUs because of the respiratory advantage (unpublished data). However, they never analysed the UC complication rate in prone position. In their experience, there was no increased risk of severe UC-related complications when positioning a newborn with an UC in the prone position. In the literature, no study has specifically described the complications associated with the prone positioning of newborns with an indwelling UC. In the guidelines from the Centers for Disease Control and Prevention, no recommendation has been made for positioning of newborns with an UC (11).

Because prone position with an indwelling UC is a common practice in most NICUs due to its respiratory advantage for the newborn, we decided to change our policy. From the start of this study it was allowed to position newborns with an indwelling UC in prone position when possible. Simultaneously, we started a prospective observational pilot study on UC complications in these newborns with UCs in situ during prone position. The primary aim of this study was to analyse the incidence of UC complications leading to catheter removal when newborns with UCs were positioned in the prone position at least 12 hours in 48 sequential hours. The secondary aim was to analyse whether local complications would increase the risk for major complications.

An approval of the medical committee of the institution or informed consent was not necessary because this observation study was based on common practice in most Dutch NICUs.

Materials and methods

Subjects

The setting was a third level 17-bed NICU with an average of 500 admissions per year.

In this prospective observational pilot study, we collected data from all newborns (from 24 weeks gestational age until term) admitted to the NICU who received an UC and nursing care in the prone position. Since prone position is not always continuously applied, only participants with at least 12 hours (3 times of 4 consecutive hours) during 48 consecutive hours in the prone position were included. Newborns who died or were transferred to another hospital with an indwelling UC for at least 48 hours and who met the criteria were also included because the effect of a minimum of 12 hours in the prone position and the possible development of local or major complications was the primary and most important goal of our study.

Excluded were: 1) newborns who did not meet the inclusion criteria of a minimum of 12 hours in the prone position over 48 consecutive hours, 2) newborns with severe persistent pulmonary hypertension, 3) newborns with abdominal surgical problems, 4) newborns who underwent Extra Corporeal Membrane Oxygenation (ECMO) treatment, 5) newborns with an UC inserted in another centre, 6) and newborns with a wet and/or red umbilical stump and rim within 12 hours after insertion of the UC.

Study design

Over a 12-months period (September 2009 - September 2010), data were collected by the investigators. Before this pilot study, all nurses were instructed in the standard care of an UC, the inclusion and exclusion criteria, the use of the checklist (Table 1), and in recognizing the complications. Prone positioning was not allowed in the first 12 hours to ensure proper observation of leakage or blood loss. Prone positioning was allowed when the umbilical stump and the rim were dry and without redness. Thus, 12 hours after insertion of the UC, the nurse initiated prone positioning when possible.

During the total observation period, each neonate was positioned for at least 12 hours of 48 consecutive hours in the prone position. Endpoints of the analysis were removal of the UC because of end of treatment or complications, transfer to another hospital, or newborns who died with an indwelling UC $>$ 2 days.

Clinical characteristics, complications, indwelling time of the catheter, hours in prone position, observation of the umbilical stump, occlusion of the infusion pump

and the reason for removal were recorded every 2 hours by the nurses using a standard manual of criteria. Reasons for removal of the UC can be divided in 2 groups: elective reasons (end of therapy, discharge and death) and non-elective reasons. Non-elective reasons included obstruction of the UC (difficult or impossible to flush, inability to administer fluid in 3 seconds), leakage/blood loss (around the UC insertion site), dislocation and CLABSI. Local complications not directly resulting in removal included redness of the skin- rim of the umbilical stump, or a moist or wet umbilical stump.

In this study we used the CLABSI definition of health care-associated infection and criteria for specific types of infection in acute setting as mentioned for patients < 1 year in the Centers for Disease Control and Prevention (CDC) (12).

CLABSI is a laboratory-confirmed bloodstream infection with a UVC and/or UAC in place for a minimum of 2 days, or in place on the day of event or the day before. Laboratory-confirmed CLABSI was defined by using one of the first 2 following definitions:

Criterion 1: one or more positive blood cultures (with the exception of skin micro-organism) not related to another infection source.

Criterion 2: clinical signs of sepsis (especially for patients < 1 year: fever or hypothermia, apnea or bradycardia), 2 or more positive blood cultures drawn on separate occasions with the same micro-organism (incl. skin micro-organism) and no other infection source. Criterion elements must occur within a timeframe that does not exceed a gap of 1 day.

An important and in practice common used criterion, but not mentioned in the CDC, is the criterion of only clinical sepsis (CSEP). In this special patient group, clinical signs are frequently the only manifestation of sepsis in the beginning and this is usually sufficient enough to start treatment with antibiotics. Sometimes it is very hard to obtain a blood culture of the small blood vessels, which frequently results in insufficient outcome for sensitive detection of bacteraemia (13). Because of this reason, we added 'CSEP' as an additional CLABSI definition. This includes clinical signs of sepsis as mentioned in criterion 2, no or 1 positive blood culture (only skin micro-organism), no other infection source other than a CVC (in situ or removed in 24 hours) and medical reasons to start sepsis treatment. This is comparable with other studies with their specific description of CSEP (14, 15).

Because in many studies only the laboratory-conformed CLABSI as mentioned by the CDC is followed, we decided to use the laboratory-confirmed CLABSI and the CSEP separately.

Thrombosis screening was only indicated when there was a clinical reason for thrombosis.

Materials and techniques

An UVC or UAC (with respectively charrières 5 and 3.5, Kendall Argyle, Tyco Healthcare, Tullamore, Ireland) was inserted under sterile conditions by trained neonatologists, nurse practitioners and residents who followed a standard protocol outlining the insertion procedure. In most cases, UAC and UVC were inserted at the same time. The tip of the UAC was positioned above the aortic bifurcation and below the origins of the renal arteries (under the 2nd lumbar vertebrae). The tip of the UVC was positioned in the inferior vena cava just before the junction with the right atrium and at the level of diaphragm. After placement of the UC, the position of the catheter tip was verified by X-ray and repositioned if necessary before parenteral nutrition or drugs were administered. The catheter was fixated with a suture through the umbilical jelly. A second fixation of the catheter with plaster (a neo-bridge) was used for extra safety (16). Twice a day, the insertion place was disinfected with a 0,5% chlorhexidine/alcohol 70% solution. In order to reduce the UC complications, especially CLABSI, our protocol prescribed that when possible an UC should be removed as soon as possible.

As a standard of care, heparin was continuously administered at a dose of 2 units per hour. Only saline with heparin was administered through the UAC. For the UVC, all medications and fluids could be used, except for blood products. The entire drip system of the UVC and UAC was replaced every 96 hours and 48 hours, respectively, according to our hospital's protocol. Drip systems for the administration of intralipid (fat solution) were changed every 24 hours. The catheter insertion site was checked every 2 hours for signs of inflammation, leakage and blood loss as part of the standard of care.

All 60 NICU nurses were competent in the care of UCs. During the primary education of NICU nurses, the nurses were trained and assessed in the care of an UC. The nurses were re-trained every 3 years. The standard care for a newborn in the supine or prone positioning did not differ. All of the patients were monitored for heart rate, respiratory rate and arterial oxygen saturation using pulse oximetry.

Mean outcome measures

The mean and standard deviation were used to describe continuous variables, which followed a normal distribution.

To check for statistical significance between categorical variables, Pearson's chi-square test or Fisher's exact-test (in case one or more cells had an expected count less than 5) was used. The relative risk was used as the association measure between a dichotomous outcome and a dichotomous risk factor. The data are presented with 95% confidence intervals (CI). A confidence interval not containing the value 1 indicated a significant relationship between the risk factor and the outcome.

Table 1 Nursing Observation Sheet: Prone Position with an indwelling UC

Patient Name:

	Date/time	Date/time	Date/time	Date/time
Prone position/supine/lateral				
Umbilical stump				
Wet/Dry				
Clear/blood/pus/Other				
Position UC in cm				
UC rim wet/dry/red				
Fixation				
Wet/Dry				
Release of fixation/plasters				
Parameters				
Heartrate/respirationrate				
O_2 saturation				
Inspiration fraction of O_2				
Respiration support				
Tidal volume				
PIP / PEEP at 12 h				
Infusion				
Occlusion alarm yes/no				
Infection				
Clinical signs yes/no				
Antibiotics yes/no				
Others				

Instructions: Fill in every care moment. Fill in with the first letter (Wet= W, Dry is D). Clinical signs only Yes/No. (detailed information will be found in the dossier)

Effects were considered statistically significant at the 0.05 threshold (α=0.05). SPSS 20.0 for Windows was used for statistical analysis.

Results

One-hundred-and-six patients were selected. Eighteen patients were excluded because they did not meet the inclusion criteria of the minimum hours in the prone position. Finally, 88 patients were included. All these newborn infants had an UVC (57% single lumen, 43% double lumen). In 44.3% cases an UAC was inserted in the same time. The mean birth weight was 1345 gram (min 400 gram, max 4220 gram). The mean gestational age was 29.6 weeks (min. 24 weeks, max 40.0 weeks, Table 2). The main reason for insertion of an UVC was the need for total parenteral feeding. There was a wide range of hours in the prone position (range 14 h - 279 h) during this study with a mean of 80.5 hours. The mean indwelling time for the UC was 6 days (mean 145 hours, range 24 hours - 336 hours) with a total of 529 catheter days.

The main reason for catheter removal was elective removal due to end of treatment (Table 3). There was no excessive blood loss or perforation of the catheter. There was a low incidence of dislocation, followed by leakage and obstruction. No thrombosis screening was indicated during this study, based on clinical signs. There were no specific occlusion alarms on the infusion pump.

Table 2 Baseline characteristics

	Patients n=88
UAC	39 (44.3)
UVC	88 (100)
Double lumen UVC	38 (43)
Birth weight (gram) mean ± SD	1345 ± 665
Gestational age (weeks) mean ± SD	29.7 ± 3.0
Indwelling time (days) mean ± SD	6.0 ± 2.8

Values are numbers (%) unless otherwise mentioned.
UAC: Umbilical Arterial Catheter, UVC: Umbilical Venous Catheter

CLABSI (laboratory-confirmed CLABSI and CSEP) was the most important complication to remove a catheter (18.2%, 30.2 per 1,000 catheter days).

However, laboratory-confirmed CLABSI was only confirmed in 9.1% of the CLABSI removals (17.0 CLABSIs per 1,000 catheter days). Only 4.5% met criterion 1 and 4.5% met criterion 2 for laboratory-confirmed CLABSI.

Coagulase-negative Staphylococcus was the most important and common cause of laboratory-confirmed CLABSI.

Table 3 Reasons for removal

	Patients n=88
CLABSI (total) - Laboratory-confirmed CLABSI - CSEP	16 (18.2) 8 (9.1) 8 (9.1)
Obstruction	1 (1.1)
Leakage	1 (1.1)
Dislocation	5 (5.7)
Perforation	0
Death/discharge	14 (15.9)
Elective removal/ end of treatment	51 (58.0)

Values are numbers (%) unless otherwise mentioned
Total UVC catheter days: 529 CLABSI: central line associated bloodstream infection, CSEP: Clinical sepsis.

There was a high incidence of local complications (redness of the umbilical rim 13.6%, persistent wet or moist umbilical stump 64.8%, pus excretion 9.1%, Table 4). Almost all umbilical stumps with a red rim had a persistent wet or moist umbilical stump.

The incidence of CLABSI (laboratory-confirmed CLABSI and CSEP) in a persistent wet umbilical was 17.9% versus 19.4% in the dry umbilical stump. This means that the relative risk for CLABSI in case of a persistent wet umbilical stump was 0.9 as compared to a dry rim (95% confidence interval 0.38-2.4, p=0.91). The relative risk for only laboratory-confirmed CLABSI in case of a wet umbilical stump compared to dry umbilical rim equals 0.6 (CI 0.15-2.1, p=0.4).

There was also no increased relative risk in case of redness of the umbilical rim (p=0.34).

In 8 cases (9.1%), we found pus excretion around the stump. In 3 cases, the UVCs were electively removed and in one case the UVC was removed because of leakage. In these 4 cases there were no clinical signs and no CLABSI developed within a timeframe of 24 hour. Only in 4 cases there was CLABSI (2 numbers laboratory-confirmed CLABSI and 2 numbers CSEP) with pus excretion. The relative risk for CLABSI in case of pus excretion was 3.3 as compared to clean umbilical stump (CI 1.40-7.93, p=0.01). The relative risk for only laboratory-confirmed CLABSI in cases of pus excretion compared to clean umbilical stump was also 3.3 (CI 0.80-13.87, p=0.1). In 7 cases of pus excretion, the umbilical surrounding was also defined as wet or moisty.

Table 4 Umbilical conditions

	Patients n=88	CLABSI (Total) n=16	Fisher Exact p-value
Red rim	12 (13.6)	0	ns
Wet or moisty rim	57 (64.8)	10 (17.9)	ns
Pus excretion	8 (9.1)	4 (50)	0.01
Dry rim	11 (12.5)	2 (19.4)	ns

Values are numbers (%) unless otherwise mentioned
CLABSI: central line associated bloodstream infection.

Only in 1 case there was also a red rim. The relative risk for pus excretion in case of a wet umbilical stump compared to a dry rim equals 4 (CI 0.515-31.06, p=0.14). However this is not significant, we assume the possibility that a wet rim will increase the risk of pus excretion.

A double lumen UVC or a simultaneous insertion of UVC and UAC did not increase the relative risk for CLABSI (laboratory-confirmed CLABSI and CSEP). This was respectively p=0.24 and p=0.48.

Also birth weight and gestational age did not influence the complication risks in this study (both P>0.5).

Because the duration of hours in prone position is depending on the indwelling time of the UC, a relative risk of complications only depended on hours in prone position can not be made.

Discussion

In this observational pilot study, no excessive blood loss, occlusion, or dislocation was seen during the prone position period. There was a relatively high incidence of CLABSI (using laboratory-confirmed CLABSI and CSEP). When using only the laboratory-confirmed CLABSI there is still a high CLABSI incidence (9%, 17 CLABSI per 1,000 central line days), compared to the literature (2.3 -17.0 CLABSI per 1,000 central line days) (2,17,18,19,20,21). Because there is no comparable study, we cannot conclude whether this high incidence is especially associated because of the prone position. However, this can be a starting point for further research.

A comparison between the studies is difficult because different CLABSI definitions have been used. Probably this can declare our high CLABSI incidence too. In 50% of

our defined CLABSIs there were laboratory-confirmed CLABSIs according to the CDC criterion.

Well-known factors that can increase CLABSI are indwelling time of an UVC, birth weight, gestational age and total parenteral feeding (2, 11,19, 22, 23).

Gestational age did not increase the risk of complications in this study. Total parenteral feeding was the main reason for UVC insertion. The need of total parenteral feeding consists in a longer indwelling time of an UVC, which probably influences the outcome (reasons for removal). The maximum indwelling time of the UVC in our study did not exceed 14 days, as described in more studies, which is relatively safe (2,11,22).

Chien et al. (2002) found an adjusted relative risk from 2.5 for the use of an UVC comparing to no UC use, causing nosocomial bloodstream infections (22). Also frequent manipulations of the UVC are a contributing factor in CLABSI. An average of 3.2 manipulations per day (0-15) is associated with a 5-fold increase in CLABSI in very low birth weight infants. We did not count the manipulations per day, so this adjusted risk cannot be mentioned, but is an important issue.

We could not find data about the incidence of local complications for UVCs, such as redness of the umbilical rim or a persistent wet umbilical stump in the literature. Therefore we assumed that the incidence of these local complications is very low or negligible. However, in this study we found a high incidence of these local complications. A reason for this high incidence might be the high humidity around the umbilical stump during prone position. Despite this high incidence, a persistent wet umbilical stump and redness of the umbilical rim were not a risk factor for major complications, such as leakage, dislocation, or CLABSI.

On the other hand, a wet umbilical stump increased the risk of pus excretion (although not significant) and pus excretion increased the risk of CLABSI significantly. Thus indirectly, a wet rim can possibly increase CLABSI. In our previous study (2005-2006) were complications in peripherally inserted central catheters and umbilical venous catheters were analysed, there was a CLABSI incidence (including laboratory- confirmed CLABSI and CSEP) in UVCs of 15% (23). This outcome is comparable with the CLABSI incidence in this study. However the laboratory-confirmed CLABSI in our previous study is lower (4.3%). Although both studies have been conducted on the same ward, we cannot make a reliable comparison while the first study was a retrospective observational study with a larger population.

This study has an important limitation. It is not a randomized study, but only an observational cohort study. The duration of prone position is also not standardized. Therefore, we consider this study as a pilot study in order to get some impression about the magnitude of the complications of UC during prone position, because there is a lack of data about it in the literature. A larger prospective randomized controlled trial of UC comparing prone and supine position can be recommended.

Conclusions

The application of prone positioning in combination with umbilical catheters in newborn infants did not result in more severe complications as compared to the literature data of UC in supine position. However, the laboratory-confirmed CLABSI incidence is relatively high. There is a high incidence of local umbilical complications without increasing the risk of major complications with exception of pus excretion from the umbilical stump. In case of pus excretion around the umbilical stump, removal of the UC should be seriously considered.

So, an umbilical catheter should not be considered as a contraindication for prone positioning when frequent observation of the umbilical rim is a standard care. A larger prospective randomized controlled trial is recommended to improve support for this conclusion.

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Central line bloodstream infection can be reduced in newborn infants using the modified Seldinger Technique and care bundles of preventative measures

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Abstract

Aim: There has been no evidence to show whether care bundles of preventive measures reduce central line associated bloodstream infection (CLABSI) in peripherally inserted central catheters using the modified Seldinger technique, which requires more specific skills than the traditional technique.
The aim of this study was address that gap in our knowledge and to determine whether other variables influenced the outcome.

Methods: This prospective observational study was conducted on a neonatal intensive care unit. We observed the incidence of CLABSI in 45 newborn infants with peripheral catheters before the introduction of bundles of preventative measures and 88 infants after the introduction.

Results: Laboratory-confirmed CLABSI decreased after the introduction of the bundles, from 12.9 per 1,000 days to 4.7/1,000 days ($p=0.09$). When we combined the rates for laboratory-confirmed CLABSI and clinical CLABSI, the incidence reduced significantly after introduction of the bundles ($p=0.02$). There were no other variables that affected the outcome.

Conclusions: Cost-effective care bundles reduced CLABSI in peripherally inserted central catheters using the modified Seldinger technique, despite the specific insertion skills that were required. The bundles of preventative measures may increase health-care professionals' awareness of the need to care for central catheters and reduce CLABSI.

Introduction

Peripherally inserted central catheters (PICCs) are widely used in neonatal intensive care units (NICUs) to administer medication and hyperosmolar solutions. The traditional catheter through needle technique, which was introduced by Shaw, is the most popular and commonly used insertion technique in most NICUs (1). The modified Seldinger insertion technique is a catheter over guide wire technique, based on the original Seldinger technique (2), and has not been widely adopted in NICUs (3). However, the modified Seldinger technique has been successfully introduced into our NICU and we now use it as the only technique for PICC insertion (4). It has many advantages, such as allowing entry into smaller or difficult to access veins, with greater success in placing PICCs and achieving a central position for the catheter in a higher percentage of cases. However, there are some disadvantages in comparison to the traditional technique. For example, medical staff need higher skill levels to use this technique, there are multiple insertion steps, the procedure takes longer and there is a risk that the guide wire may perforate vessels (5). These may all increase the risk of central line associated bloodstream infection (CLABSI). In the literature we found that the CLABSI incidence ranged from 3.8 to 18.1 in all vascular devices in newborn infants (6). However, we were unable to find published data on CLABSI incidences in PICCs, which are only inserted using the modified Seldinger technique in newborn infants. In the context of patient safety, nosocomial infections such as CLABSI are considered to be a preventable medical complication (7). Therefore, numerous interventions have been introduced to reduce the incidence of CLABSI in all vascular devices and this has led to an impressive decrease in CLABSI (8,9,10). However, due to the differences in insertion technique between the traditional and the modified Seldinger technique, we hypothesised that preventive bundles in PICCs using the modified Seldinger technique would lead to a less impressive decrease of CLABSI in comparison to the traditional technique. For this reason, we conducted a study with the primary objective of observing the CLABSI incidence after the introduction of preventive care bundles during the insertion procedure using the modified Seldinger technique, together with the maintenance period of the PICCs. The secondary objective was to observe whether the known variables of birth weight and postnatal age at insertion time, as detailed in the literature, might influence the incidence of CLABSI.

Materials and methods

Subjects

We performed a prospective observational cohort study in a tertiary-level 17-bed NICU with an average number of 500 admissions per year. We initiated the study in the pre-intervention period (October 2009 - April 2010) and ended it in the post-

intervention period (January 2011-December 2011). The preventive care bundles were introduced between April 2010 and January 2011.

The study included all newborn infants born between 24-42 weeks of gestation, with an indwelling PICC inserted using the modified Seldinger technique, which was then later removed in our NICU. The exclusion criteria were 1) newborn infants with a PICC inserted in another NICU, because possible differences in the insertion procedure may have affected the CLABSI rate, 2) newborn infants where the indwelling time of the PICC shorter was than 24 hours, because such a short indwelling time may have influenced the outcome, assuming that CLABSI will never occur within 24 hours of insertion, and 3) newborn infants undergoing extra corporeal membrane oxygenation treatment, which induces clotting activities that may result in an increased risk of thrombi formation. These newborn infants were treated with continuous heparinization in order to reduce the risk of thrombi formation (11), as this can also increase the risk of CLABSI (12).

Study design

During the pre-intervention period we recorded the following observations: the clinical characteristics of gestational age and birth weight, the reason for insertion, age at insertion, insertion location, indwelling time, the reason for removal and CLABSI signs for 48 hours after removal of the PICC. There were no changes in material, protocols and hygienic procedures and all nursing and medical staff was aware of this observation period.

During the 6-months intervention period, the researchers and a group of 8 nurses with special responsibility for infusion care, known as the infusion team, introduced bundles of preventive measures to the nursing team and medical staff through on-the-job training and training programmes.

These preventative bundles included: 1) sharing the analysis of the pre-intervention period with the whole NICU team of nurses, hygienist, neonatologist, residents and consultants in paediatric infectious diseases to increase their joint responsibility in preventing CLABSI; 2) introducing an insertion-checklist; 3) adapting the existing protocols for insertion procedure and daily nursing care to the most recent evidence-based developments with special emphasis on hygiene. This involved a clear demarcation of the working area during the insertion procedure with mobile screens, temporary closure of the entrance to the unit in question and sharper protocols for hand hygiene, disinfecting the catheter hub and hygiene protocols during the insertion procedure and 4) standard daily assessment by both, nurses and neonatologists, to determine whether the PICC was still required.

The post-intervention period used the same insertion material, techniques and observation list as the pre-intervention period, but the procedures were updated as described in the bundles.

Data collection

Data were collected by the 2 researchers (IA and NS), together with support from the infusion team. An assessment for inter-rater reliability was not carried out. However, all results were double-checked by the researchers, so that the possibility of mis-classification was low. The duration of an indwelling PICC was calculated in days, from insertion to removal. The reasons for removal were end of treatment, death, transfer to another department, CLABSI and other complications, such as obstruction of the PICC (difficult or impossible to flush or the inability to administer fluid in 3 seconds) leakage, or blood loss around the insertion site and thrombosis. Thrombosis screening was only indicated when there was a clinical suspicion of thrombosis. The catheter insertion site was observed every 8 hours for signs of inflammation or leakage.

Laboratory-confirmed CLABSI was defined according to the most recent definition of the US Centers for Disease Control and Prevention (CDC) (13). However, this may not have covered all CLABSIs in the NICU. Clinical signs are frequently the only manifestation of sepsis in newborn infants and this is usually sufficient to start treatment with antibiotics. Sometimes it is difficult to obtain the blood volume needed for a reliable blood culture because of the small catheter lumen, resulting in an insufficient blood culture for sensitive detection of bacteremia (14). As Horan et al. (15) described, clinical sepsis (CSEP) may only be used to report primary bloodstream infection in neonates and infants under the age of 1 year (15). In our study, CSEP included at least 1 of the following clinical signs - fever, hypothermia, apnea or bradycardia - with no other recognised cause than the PICC. Also physicians instituted treatment for sepsis although there was an absence of a blood culture or no detectable organisms in the blood culture, except for 1 culture of skin organisms. In order to meet the CLABSI criteria, there must not be more than a 1-day gap between the various elements occurring. Because laboratory-confirmed CLABSI is used in most studies, we also used this as our primary CLABSI definition. However we did not ignore CSEP, so overall CLABSI comprised laboratory-confirmed CLABSI plus CSEP.

Materials and techniques

A 22 gauge, 20cm long polyurethane single lumen catheter (Leaderflex 22 Gauge, Vygon, Aachen, Germany) was inserted as a PICC by neonatologists under aseptic conditions and aseptic barrier precautions. In most cases the basilica, cephalic and greater saphenous vein were used to provide vascular access for the PICC insertion. Occasionally, the right temporal vein was used. The catheter was covered by a semipermeable dressing (Tegaderm, 3M Health Care, St. Paul, MN, USA) after insertion, which was only changed if it became detached from the skin. The hubs were scrubbed using 0.5% chlorhexidine in 70% alcohol. Heparin was continuously administered at a dose of 2 units per hour to prevent catheter occlusion (12).

Because the small lumen of the PICC has an increased risk of obstruction, administration of blood products and aspiration of blood for analysis were only performed when it was absolutely necessary. The entire infusion system of the PICC was changed and disinfected every 96 hours as standard care. The infusion system for administration of intralipid was changed every 24 hours in line with hospital hygiene policy.

Data analysis

SPSS 20.0 for Windows was used for the statistical analysis. A Fisher exact test was used to assess the statistical significance of differences between categorical variables and a Cox regression analysis was used to correct possible confounders, such as birth weight and postnatal age at insertion. When no confounders were found, we preferred to use the Kaplan-Meier survival test to evaluate the difference in survival rates between the pre-intervention and post-intervention periods, where the event was defined as laboratory-confirmed CLABSI. Additionally, the analysis was repeated using overall CLABSI (laboratory confirmed CLABSI plus CSEP) as the event. The relative risk was used as the association measure between a dichotomous outcome and a dichotomous risk factor and is presented with 95% confidence intervals (CI). Effects were considered statistically significant at a threshold of 0.05 (α=0.05). Mean and standard deviation were used to describe continuous variables, which followed a normal distribution. The incidence of infection was expressed as infection episodes per 1,000 catheter days.

Results

During the 6-months pre-intervention period, we included 43 patients with a total of 45 PICCs and 463 catheter days. In the 12-months post-intervention period, we included 82 patients with a total of 88 PICCs and 858 catheter days. There were no statistical significant differences in the baseline characteristics between the 2 groups, such as gestational age, birth weight, postnatal age at time of PICC insertion and indwelling time (Table 1).

The most common reason for catheter placement was the need for total parenteral nutrition and intravenous medication administration for longer than 3 days. The most important reason for removal was the end of treatment. There were no significant differences in the incidence of obstruction, leakage or thrombosis between the groups (Table 2).

The incidence of laboratory-confirmed CLABSI was 12.9 per 1,000 catheter days (13.3%, CI 5.05 - 26.97) in the pre-intervention period and 4.7 per 1,000 catheter days (4.5%, CI 1.25 - 11.23) in the post- intervention period (p=0.09). Although this finding was not statistically significant, it might have indicated a declining trend in CLABSI.

Table 1 Baseline characteristic of the newborn infants with peripherally inserted central catheters inserted using the modified Seldinger technique during the pre-intervention and post-intervention periods

	Pre-intervention period (n=45)	Post-intervention period (n=88)	t-test p-value
Gestational age (weeks)	30.7 ± 4.3	32.1 ± 4.9	0.10
Birth weight (grams)	1460 ± 796	1787 ± 1053	0.07
Postnatal age at insertion (days)	8.5 ± 9.3	10.3 ± 12.8	0.40
Indwelling time (days)	10.3 ± 5.5	9.9 ± 6.2	0.70

Values are mean ± standard deviation.

Table 2 Reasons for the removal of peripherally inserted central catheter during the pre-intervention period (October 2009 – April 2010) and the post-intervention period (January 2011 – December 2011)

	Pre-intervention period (n=45)	Post-intervention period (n=88)	Fisher Exact p-value
End of treatment	22 (48.9)	41 (46.6)	0.85
Death/transferred	9 (20)	31 (35.2)	0.07
Other complications	0	6 (6.8)	0.10
Indwelling duration (days)	463	858	
Only laboratory confirmed CLABSI	6 (13.3)	4 (4.5)	0.09
Only laboratory confirmed CLABSI per 1,000 catheter days	12.9	4.7	
Overall CLABSI	14 (31.1)	10 (11.5)	0.01
Overall CLABSI per 1,000 catheter days	30.2	11.6	

Values are numbers (%) unless otherwise mentioned
Overall CLABSI = laboratory-confirmed CLABSI (central line associated bloodstream infection) and clinical sepsis

However, there was a significant decline (63.0%) in overall CLABSI (laboratory-confirmed CLABSI plus CSEP) with an overall CLABSI incidence in the pre- intervention period of 30.2 CLABSIs per 1,000 catheter days (31.1%, CI18.2 - 46.7) and 11.6 CLABSIs per 1,000 catheter days (11.5%, CI 5.6 - 19.9, p=0.01) in the post-intervention

period. A Cox regression method was used to correct for possible variables that might have influenced the CLABSI outcome, such as birth weight and postnatal age at insertion. Birth weight (p=0.74) and postnatal age at insertion (p=0.62) did not have any effect on CLABSI.

Kaplan-Meier survival analysis showed no significant difference in PICC indwelling time between the 2 groups, using laboratory-confirmed CLABSI (p=0.15, Figure 1), but it seemed that there was a trend of shorter PICC indwelling time in the pre-intervention period than the post-intervention period.

A significant difference was found when using overall CLABSI – laboratory-confirmed CLABSI plus CSEP - as the event for removal in this survival analysis (p=0.02) (Figure 2). In the majority of the CLABSIs, we found a *coagulase negative Staphylococcus* (50%) followed by *Staphylococcus aureus* (16.7%) and others (13.3%) in the blood cultures. Five blood cultures were negative (20.8%) with one Bacillus found on the catheter tip.

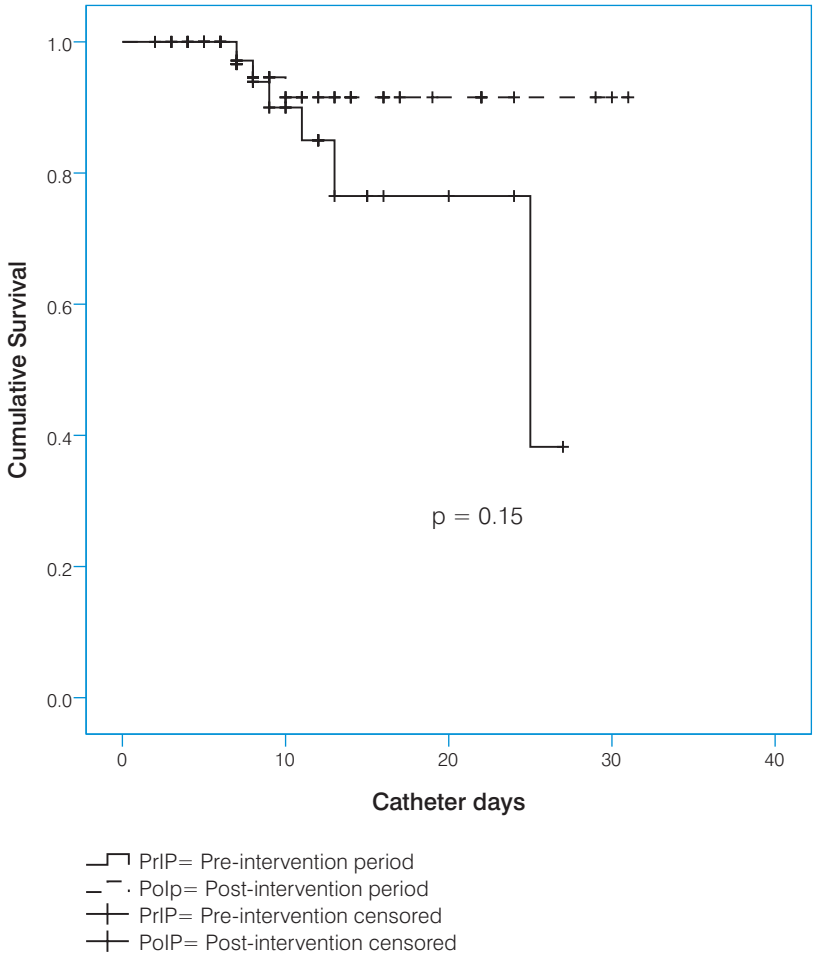
Discussion

As far as we know, this is the first study to report a substantial reduction of CLABSI when using preventive CLABSI bundles in newborn infants with PICCs inserted using the modified Seldinger technique. We cannot say whether the longer insertion time and the multiple steps used in the modified Seldinger insertion technique affected the CLABSI decline and we cannot draw a clear comparison between a traditional insertion technique and the modified Seldinger technique, as we only used the modified Seldinger technique on our ward. However, the magnitude of CLABSI reduction in this study seems comparable with PICCs inserted using the traditional technique, as reported in the literature.

The most important reason for the substantial decline of CLABSI is probably due to sharpening the hygiene protocols in the team and more uniform procedures and care in the PICC insertion together with the PICC maintenance. Sharing the results from the pre-intervention period with the team promoted the importance of hygiene. Several studies have shown a remarkable decline in CLABSI when healthcare providers participate in national surveillance and when dedicated PICC maintenance teams or specific preventive bundles are introduced (6,16,17,18). It is also conceivable that our team of neonatologists had developed greater experience and skill in placing the PICCs between the pre-intervention and post intervention periods and this might have played a role in reducing CLABSI in the post-intervention period.

The incidence of laboratory-confirmed CLABSI in the post-intervention period (4.7 CLABSI per 1,000 catheter days) is low compared to the 17.0 per 1,000 catheter days in PICCs in surgical and medical newborn infants quoted by the Njere et al. study (19). However, comparing the CLABSI incidence with these results is difficult,

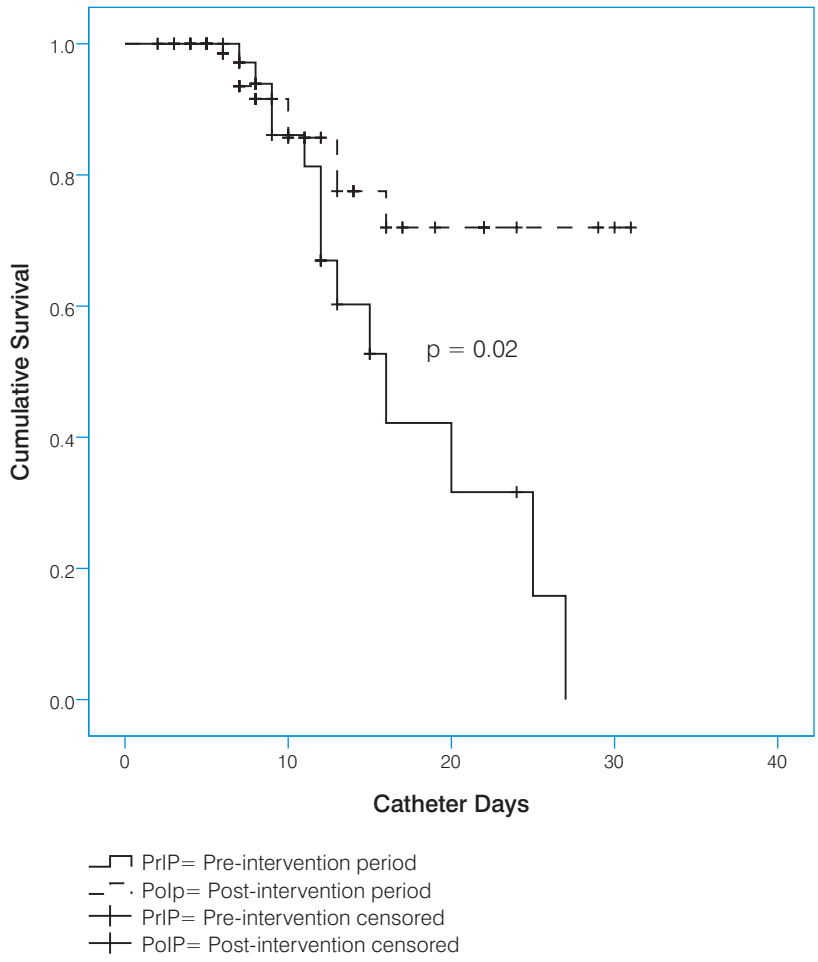
Figure 1 Kaplan-Meier using just laboratory-confirmed CLABSI as event



due to the different definitions of CLABSI used by studies. In this study we demonstrated the difference between the CLABSI laboratory-confirmed rates, according to the CDC criteria, and the combination of laboratory-confirmed CLABSI and CSEP.

We feel that the CSEP group cannot be ignored, as it is not currently possible to determine whether bacteraemia is present or not. It is possible that in the future new reliable methods will be developed using minimal blood volume to detect bacterial deoxyribonucleic acid, enabling us to detect bacteraemia in the CSEP group.

Figure 2 Kaplan-Meier survival using overall CLABSI (laboratory-confirmed CLABSI and CSEP as event



Birth weight and postnatal age at insertion did not affect the outcome in this study, in line with the studies by Yumani et al. (6) and Sengupta et al. (20). They suggested that catheter duration was a very important risk factor for developing CLABSI in PICCs. This means that in order to prevent CLABSI, daily evaluation is necessary to determine whether a PICC is still necessary or not.

As Suresh stated, it is important to change the culture and attitudes of healthcare workers so that they see CLABSI as preventable in NICU patients rather than an inevitable complication (7). Maintaining this awareness and responsibility might be a

great challenge in the future. In our study we did not measure the effect of this intervention on the cost of healthcare. According to the study by Shorr et al. (21), published in 2003, the estimated cost of a CLABSI for adults was US $10,920 (22). The cost for newborn infants is unknown, but we assumed to be at least the same or higher. The estimated cost of the bundles in our study was less than US $1,000 per year. So, the cost saving in our NICU due to decreased CLABSI was estimated to be about US $196,560 per year.

The most important limitation of our research is the fact that it was an observational study with a small population. It is probably that the small cohort size was the reason that we could not find a significant difference between the 2 periods in the laboratory-confirmed CLABSI group, even though CLABSI declined by more than 60%. Another limitation is the absence of an inter-rater reliability test for classifying the CLABSI criteria. However, the double-checking carried out by the researchers should minimise misclassification. In addition, the decision about when to remove the PICC was a personal decision made by the attending neonatologist and this may have influenced the indwelling time of each PICC. There was no change in the team of attending neonatologists during this study, so the personal differences in decision-making did not seem to change during this period.

Despite these limitations, this study offers a good starting point for further research and the development of high-quality improved interventions that could be extended to other Dutch NICUs. We believe that a large randomized controlled trial, with evidence-based interventions that compare the modified Seldinger technique with the traditional technique, would provide the most reliable outcome.

Conclusions

Despite the need for specific insertion skills, the introduction of care bundles of preventive measures significantly reduced the CLABSI incidence in PICCs inserted using the modified Seldinger technique. This reduction is comparable to the CLABSI incidence reported in the literature for PICCs inserted into newborn infants using the traditional technique. It is probably more important to ensure that the introduction of the bundles increases awareness of potential CLABSI incidences, as this will help team members to achieve state-of-the-art care.

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6

Preventive bundles as a measure to decrease central line associated bloodstream infection in umbilical venous catheters in newborns

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Abstract

Aim: The principal aim of this study was to determine whether preventive bundles can reduce central line associated bloodstream infection (CLABSI) in umbilical venous catheters. A secondary goal was to observe whether other variables may influence the outcome.

Methods: This prospective observational study was conducted in a single centre neonatal intensive care unit. The incidence of laboratory-confirmed CLABSI and clinical sepsis in newborn infants with umbilical venous catheters was observed before (pre-intervention period) and after (post-intervention period) the introduction of preventive bundles and the use of a new insertion tool. A large team with different practical skills inserted the umbilical venous catheters.

Results: In the pre-intervention period 72 UVCs and in the post-intervention period 149 UVCs were recorded**.** We observed no reduction in the incidence of laboratory-confirmed CLABSI after introduction of the bundles (pre-intervention group 10.0 /1,000 days versus post-intervention group 10.8/1,000 days p=1.00). There was also no change in the incidence of laboratory-confirmed CLABSI and clinical sepsis together (pre-intervention group 18.0/1,000 days versus post-intervention group 26.4 /1,000 days p=0.36). Postnatal age and at insertion and birth weight were independently associated with CLABSI.

Conclusions: Preventive bundles do not reduce the CLABSI incidence in umbilical venous catheters in this study. Introduction of a new insertion tool at the same moment may have affected this outcome negatively. The insertion of the UVC by a large medical and nursing team with differences in practical skills and the older postnatal age at insertion in the post-intervention period could also potentially have influenced the outcome of this study.

Introduction

An umbilical venous catheter (UVC) is commonly used in newborn infants in a neonatal intensive care unit (NICU) to administer drugs, fluids and parenteral nutrition. The easy use of the umbilical venous access directly after birth avoids painful skin punctures needed for a peripheral venous access, a peripherally inserted central catheter (PICC) or a surgically inserted central venous catheter. UVCs are usually inserted during the first hours of life until 2 days after birth. It is not recommended to use an umbilical vein for UVC insertion 2 days or later after birth because of the assumed increased risk of central line associated bloodstream infection (CLABSI) due to the bacterial colonization of the necrotic stump. Unfortunately, the use of UVCs is not without risks. Several complications of UVCs have been described, such as CLABSI, occlusion, thrombosis, dislocation, extravasation, and phlebitis (1,2,3,4,5,6,7). CLABSI is the most common serious complication. The occurrence of CLABSI varies from 1.7 to 22.0 per 1,000 catheter days (7,8,9). In a retrospective study in 2005-2006 we found a CLABSI incidence of 21.4 per 1,000 catheter days in UVCs in our NICU (10). An umbilical stump is assumed to be a potential risk for CLABSI. Micro-organisms can easily gain access through the entry site of the venous catheter into the vein. Chien et al. reported an adjusted relative risk of 2.0 for UVC related nosocomial CLABSI in newborns as compared to non-catheter related nosocomial infection (8). Factors such as indwelling time, postnatal age at insertion, the use of total parenteral nutrition and birth weight are associated with increased risk for CLABSI (7,8,11).

Nosocomial infections, like CLABSI, are considered as a preventable medical complication (12). Several studies show an impressive CLABSI decrease after the introduction of preventive bundles, interventions or participation in a national survey (7,13,14,15).

We therefore conducted a study with the primary objective of observing the CLABSI incidence after the introduction of preventive care bundles during the insertion procedure and indwelling period of the UVCs. The secondary objective was to observe whether the known variables like birth weight and postnatal age at insertion time, as detailed in the literature, might influence the incidence of CLABSI.

Materials and methods

Subjects

In a 17-bed tertiary-level NICU with an average of 500 admissions per year we performed a prospective observational cohort study. The pre-intervention period was started in October 2009 and ended in April 2010. Preventive bundles and new insertion tool for UVCs were introduced between April 2010 and January 2011. After

introducing these bundles, we started with a 12-months post-intervention period from January 2011 to December 2011.

All newborn infants (born between 24 - 42 weeks gestational age) with an indwelling UVC were included. Excluded were 1) newborns with the indwelling time of the UVC shorter than 24 hours, because such short indwelling time may influence the outcome, assuming that CLABSI will never occur within 24 hours after insertion, and 2) newborns with Extra Corporeal Membrane Oxygenation (ECMO) treatment, because ECMO will induce clotting activities which may result in increased risk for formation of thrombi. Therefore, these newborns were treated with continuous heparinization in order to reduce the risk for thrombi (16). Thrombi can also increase the risk of CLABSI (17).

Study design

Pre-intervention period: In the pre-intervention period we used an observation list which reported clinical characteristics, gestational age, birth weight, reasons for insertion, age at insertion, indwelling time, reason for removal and CLABSI signs until 48 hours after removal of the UVC. There were no changes in protocols and hygienic procedures. The medical and nursing staff were aware of this observation period.

Interventions: A new all-in-one insertion tool for UVC and umbilical arterial catheter was introduced. This consisted of a total package of all disposable materials with exclusion of the catheters, gloves, gown, cap and mask. Previously we used a non-disposable set with re-sterilization after use. In addition, preventive bundles were developed. These bundles included: 1) sharing the analysis of the pre-intervention period with the whole NICU team (nurses, hygienist, neonatologist, residents and consultants in pediatric infectious diseases) to increase the responsibility in preventing CLABSI; 2) introducing a checklist during insertion procedures; 3) adapting the existing protocols of insertion procedure and daily nursing care to the most recent evidence based recommendations with special emphasis on hygiene. This means a clear demarcation of the working area during the insertion procedure with mobile screens, temporary closure of the entrance of the unit in question and sharpening of the hygienic rules such as hand hygiene and disinfection of the insertion site during insertion procedure, and 4) completing the standard daily assessment (by nurse and neonatologist) whether the UVC is still needed or not.

For a period of 8 months, the researchers and a group of 8 nurses with responsibility for infusion care (infusion team) introduced the new material and the preventive bundles to the nursing team and medical staff via training programs.

Post-intervention period: During the post-intervention period, the same insertion technique and observation list were used as described in the pre-intervention period. In the post-intervention period the procedures were updated as described in the bundles.

Data collection

Data were collected by the 2 investigators (IA and NS). The infusion team supported them. An assessment for inter-rater reliability was not made. However, all results were double checked by the investigators. Therefore the possibility of misclassification was assumed to be low.

The duration of an indwelling UVC was calculated in days, counting from UVC insertion until UVC removal. Elective reasons for removal were end of treatment or removal because of our protocol (removal of the UVC when possible at day 7). Non-elective reasons for removal were CLABSI and other complications such as obstruction (difficult or impossible to flush, inability to administer fluid in 3 seconds), leakage or blood loss around the insertion site, and thrombosis. Thrombosis screening was only indicated when there was a clinical suspicion of thrombosis. During every nursing care moment (2 - 4 hours), the catheter insertion site was observed for signs of inflammation or leakage.

We defined laboratory-confirmed CLABSI according to the most recent definition of the Center for Disease Control and Prevention (18). However, this may not cover clinical sepsis in newborn infants. Using only laboratory-confirmed CLABSI, the actual rate of CLABSI may be underestimated because it is sometimes difficult to obtain the required blood volume for a reliable blood culture in the tiny neonates (19). A small blood volume is frequently insufficient for sensitive detection of bacteremia (20). As reported by Horan et al. clinical sepsis (CSEP) may be used only to report primary bloodstream infection in neonates and infants (21). In our study we used a derivative of this CSEP definition and included:

- at least 1 of the following clinical signs: fever, hypothermia, apnea, or bradycardia, with no other recognized cause as the UVC,
- one positive blood culture with a skin micro-organism, or blood culture not done, or no organisms detected in blood culture,
- no apparent infection at another site,
- the attending physician institutes treatment for sepsis.

All elements used to meet the CLABSI criterion must occur within a timeframe that does not exceed a gap of 1 day. Although CSEP is common in our NICU, we used laboratory-confirmed CLABSI as primary outcome. As secondary outcome we use the laboratory-confirmed CLABSI and the CSEP together.

Materials and insertion procedure

An UVC (single or double lumen, Charrière 5 Kendall Argyle, Tyco Healthcare, Tullamore, Ireland) was inserted under aseptic conditions by a team consisting of neonatologists, nurse practitioners and residents. Neonatologists and nurse practitioners are permanent members of the team. The residents rotate within a period between 2 and 12 months. Residents get on-the-job training by neonatologists

and nurse practitioners in the insertion procedure following a standard protocol. The tip of the UVC was positioned in the inferior caval vein just before the junction with the right atrium at the level of the diaphragm. The position of the tip was verified by X-ray and repositioned if necessary before parenteral nutrition or drug administration were started. The catheter was fixed with a suture through the umbilical jelly. A second fixation of the catheter with plaster (a neo-bridge) was used for extra safety (22). The insertion place was disinfected twice a day using 0.5% chlorhexidine/alcohol 70% solution. In order to reduce UVC-related complications, especially CLABSI, an UVC should be removed as soon as possible and preferably before day 7.

Heparin (2 units per hour) was continuously administered to prolong the UVC patency (17). Due to the small lumen of the catheter, administration of blood products or aspiration of blood for laboratory analysis was only allowed when it was absolute necessary because of the risk of catheter obstruction.

The entire drip system of the UVC was replaced every 96 hours according to the hospital protocol. Drip systems for the administration of fat solution were changed every 24 hours.

Prone position of the newborn was allowed after confirmation of a good tip position of the catheter and when the umbilical rim is dry.

All 60 NICU nurses were competent in the care of UVCs. During the primary NICU nurses education, nurses were trained in the care of an UVC. They were re-trained every 3 years.

Data analysis

SPSS 20.0 for Windows was used for statistical analysis. To assess the statistical significance of differences between categorical variables, a Fisher exact test was used. As a measure of the association between a dichotomous outcome and a dichotomous risk factor, the relative risk was used, presented with a 95% confidence interval (CI). To assess the difference of a metric variable in 2 groups the t-test was used.

To study the occurrence of CLABSI in time we used survival analysis. In case only the 2 intervention periods were compared with each other, two Kaplan-Meier survival curves were built and compared with each other using the test of Gehan. In this test the difference in survival rates between the pre-intervention period and post-intervention period in which the event was defined as laboratory-confirmed CLABSI in the primary outcome and as overall CLABSI (laboratory-confirmed CLABSI and CSEP) in the secondary outcome, was evaluated. When correction for possible confounder seems necessary in the survival analysis the Cox regression analysis model was used.

Effects were considered statistically significant at 0.05 threshold ($\alpha=0.05$). Incidence of an infection was expressed as infection episodes per 1,000 catheter days.

Table 1 Baseline characteristics

	Pre-intervention period n=72	Post-intervention period n=149	t- test p-value
Birth weight (grams)	1808 ± 972	1886 ±1057	0.60
Gestational age (weeks)	31.4 ± 4.7	32.1 ± 5.0	0.80
Indwelling time (days)	6.9 ± 3.3	6.8 ± 3.6	0.85
Postnatal age at insertion (days)	0.43 ± 0.7	0.74 ± 1.1	0.03

Values are mean ± standard deviation.

Results

During the 6-months pre-intervention period, 72 UVCs were included with a total of 499 catheter days. In the post-intervention period, 149 UVCs were included with 1,019 catheter days. An umbilical arterial catheter was also inserted in almost 50% of the UVCs in both groups.

Table 2 Reasons for removal

	Pre-intervention period n=72	Post-intervention period n=149	Fisher Exact p-value
Elective removed	39 (54.1)	92 (61.8)	0.31
Discharge or death	18 (25.0)	26 (17.4)	0.21
Leakage	1 (1.4)	0	0.32
Dislocation	5 (6.9)	4 (2.7)	0.16
Overall CLABSI	9 (12.5) 18.0/1,000 catheter days	27 (18.1) 26.4/1,000 catheter days	0.36
- Laboratory confirmed	5 (6.9) 10.0/1,000 catheter days	11 (7.4) 10.8/1,000 catheter days	1.00
- CSEP	4 (5.5) 8.0/1,000 catheter days	16 (10.7) 15.7/1,000 catheter days	0.36

Values are numbers (%) unless otherwise mentioned
CLABSI=central line associated bloodstream infection.

Table 3 Micro-organisms in blood culture

	CLABSI pre-intervention period n=9	CLABSI post-intervention period n=27
Coagulase negative Staphylococcus	5 (55.6)	10 (37.5)
Staphylococcus epidermidis	1 (11.1)	1 (3.7)
Staphylococcus haemolyticus	0	1 (3.7)
Staphylococcus aureus	0	4 (14.8)
Blood culture negative	3 (33.3)	8 (29.6)
Unknown	0	3 (11.1)

Values are numbers (%) unless otherwise mentioned
CLABSI=central line associated bloodstream infection.

There was no significant difference between the pre-intervention group and the post-intervention group for birth weight, gestational age, and the mean catheter indwelling time. However, there was a significant difference in the postnatal age at insertion between both periods (p=0.03, Table 1). The indwelling UVC remained in situ longer than 7 days in 44.4 % in the pre-intervention versus 39.6% in the post-intervention period with a maximum of 16 days in the pre-intervention period and 37 days (1 UVC) in the post-intervention period.

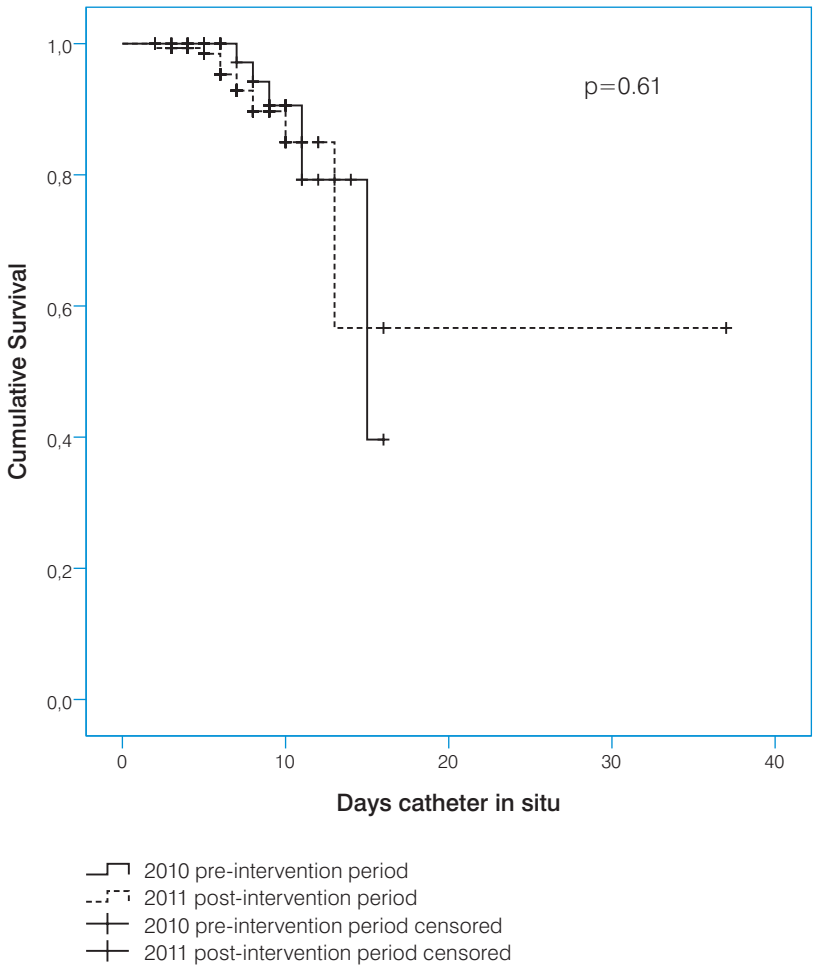
The most important reason for UVC removal was elective removal due to end of treatment or following our protocol. The most important complication that resulted in non-elective removal was CLABSI, followed by dislocation and leakage. Leakage was only described in the pre-intervention period.

In the pre-intervention period laboratory-confirmed CLABSI was 10.0 per 1,000 catheter days, (6.9%) versus 10.8 per 1,000 catheter days in the post-intervention period (7.4%, p=1.0). There was no statistically significant difference in overall CLABSI (laboratory-confirmed CLABSI and CSEP) between pre-intervention and post-intervention period (18.0 per 1,000 catheter days versus 26.4 per 1,000 catheter days, p=0.36).

When using only laboratory-confirmed CLABSI as event, the Kaplan-Meier survival plot shows similar proportions of UVC remaining patent up in both periods (p=0.61 Figure 1).

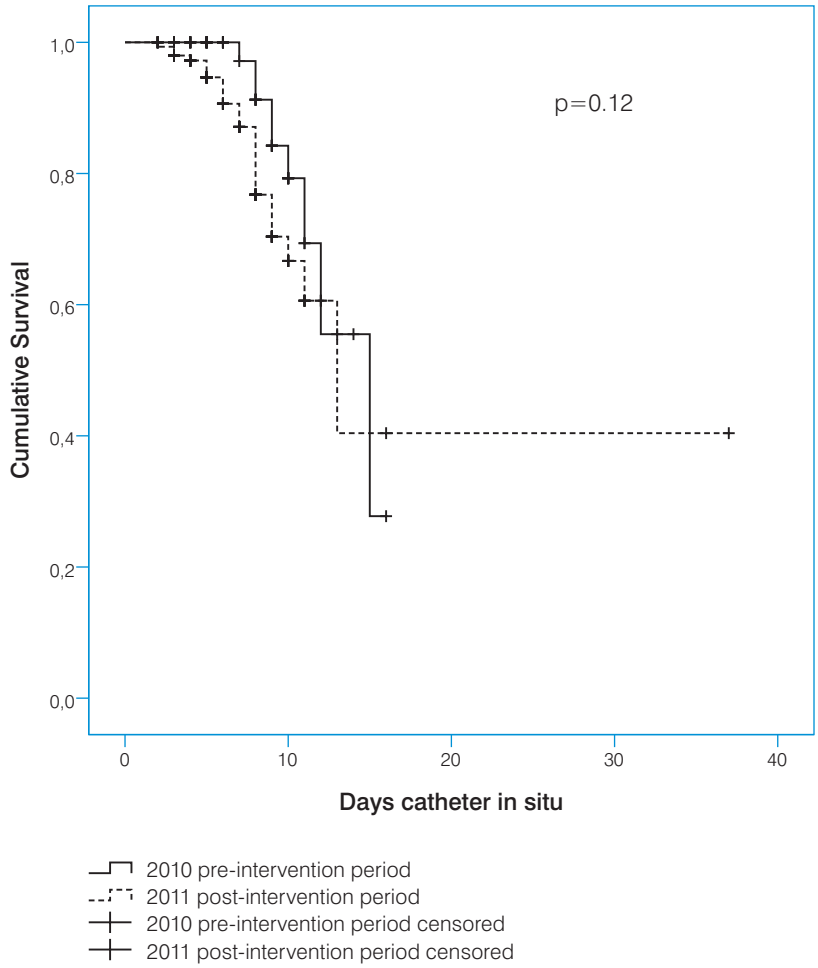
Using the Kaplan-Meier survival plot with the overall CLABSI as event, again we did not find a significant difference between the pre- and the post-interventional period (p=0.12 Figure 2).

Figure 1 Kaplan-Meier survival: event is laboratory-confirmed CLABSI



To correct for possible confounders (birth weight and postnatal age at catheter insertion), which may influence the CLABSI outcome, a Cox regression method was used. When analysing the influence of birth weight on the overall CLABSI, the Cox regression analysis showed a significant risk for birth weight (Hazard Ratio 0.9996, CI 0.999 - 1.000). This looks like a small effect, but is definitely substantial. For example, the Hazard for overall CLABSI for a newborn infant with a birth weight of 2,500 gram was 0.55 times smaller when compared to a newborn with birth weight of 1,500 gram. Postnatal age at insertion did influence the overall CLABSI outcome with a relative risk of 1.4 (CI 1.18 - 1.78).

Figure 2 Kaplan-Meier survival: event is overall CLABSI (laboratory-confirmed and clinical CLABSI)



A *coagulase negative Staphylococcus* was found in most of the blood cultures (pre-intervention period 55.6% versus 37.5% in the post-intervention period). Only in the post-intervention group we found *Staphylococcus aureus* related CLABSI (14.8%). In the pre-intervention group 33.3% of blood cultures were negative versus 29.6% in the post-intervention group (Table 3).

Discussion

In this study we found no difference in CLABSI incidence in UVCs after introduction of the bundles. This is interesting because in several studies participation in a national survey alone increased the awareness of the caregivers, resulting in more attention for hygienic rules and diminishing CLABSI incidences (23,24). Even when bundles were used to reduce CLABSI in peripherally inserted central catheters (PICCs) using the modified Seldinger technique, which is a more difficult insertion technique when compared with UVC insertion, there was a remarkable decrease (25).

One explanation for our observation is the fact that the group who inserted UVCs (residents, nurse practitioners and neonatologists) was larger than the group who inserted PICCs (only neonatologists). In addition, residents rotated frequently during this study, and therefore missed the training of preventive bundles from the beginning when compared to the PICC study. The residents were trained on the bedside by a neonatologist or nurse practitioner in UVC insertion. This may have resulted in a prolonged insertion time, more (unnecessary) manipulations, and more people around the aseptic procedure, thus influencing CLABSI outcome. The reduction in clinical experience and expertise may have influenced CLABSI risk and explain the difference in CLABSI decrease as compared to our previous study with PICCs (25). A dedicated infusion team, responsible for insertion and care for the central venous catheter, may further reduce the CLABSI incidence because of their increased clinical experience (26).

The introduction of a new insertion tool in the intervention period may also have negatively affected the outcome, although we assume that an 8-months intervention period must have been enough to acquire sufficient skills by the team in the use of this new insertion tool. In practice the insertion pincet of the new system was not as well manufactured as the one used previously. This may have prolonged the insertion time and increased the frequency of manipulations on the umbilical stump.

Because of the assumed increase of CLABSI in prolonged UVC indwelling time, our protocol recommends removal of an UVC before day 7. However in practice, almost 50% of the UVCs remain in situ longer than 7 days. This is comparable with data from our retrospective study that an indwelling time of 14 days was relatively safe when compared to the complication incidence of PICCs (10). There is also no difference in the percentage of UVCs with indwelling time more than 7 days between pre-intervention and post-intervention periods. However, unnecessary prolonged indwelling time must be prevented (2,10,27). A short indwelling time is always the best strategy to reduce CLABSI.

Shahid et al. discussed the true need of UVCs in newborns and suggested that the number of UVCs could be reduced. They evaluated the proportion of newborns with gestational age < 33 weeks who received an UVC before and after the introduction

of guidelines for insertion. The new guidelines contained clear indications for the use of UVC placement on the basis of gestational age, severity of illness and the ease of establishing a peripheral intravenous catheter. After the introduction, the proportion of newborns receiving UVCs decreased significantly without an increase of newborn infants receiving a PICC. However, the CLABSI incidence was similar between the pre-intervention period and the period after improvements (28). So, although the number of UVC insertion decreased impressively, the CLABSI incidence did not change.

Birth weight and postnatal age at insertion were factors independently associated with CLABSI. More studies showed an increased risk in children with low birth weight (2,11). In the current study, birth weight and postnatal age at insertion did influence the overall CLABSI outcome. However, there was no significant difference in birth weight between the 2 periods. Therefore we cannot conclude that birth weight affects CLABSI incidence in the post-intervention period. But there was a significant difference between the 2 periods concerning the postnatal age at insertion of the UVC. Most of the UVCs were inserted in the first 48 hours in both groups. However in the post-intervention period there were more UVCs inserted after 48 hours postnatal age than in the pre-intervention period. This may have had a negative influence on the CLABSI incidence.

Although no reduction of CLABSI was found after implementation of preventive bundles the laboratory-confirmed CLABSI incidence in our study is comparable with that in the literature. The continuous rotation of residents who were not involved from the onset of the study may have been a risk factor for the increased CLABSI incidence. Involvement from the beginning might have created awareness that CLABSI is preventable instead of assuming that CLABSI is an inevitable complication in the care of newborn infants (12). Therefore we recommend that all new healthcare workers take an obligated training program to prevent complications such as CLABSI on the NICU.

This study had several limitations. The most important is the fact that this is an observational study with a small number of patients. Using a larger population may provide a more reliable outcome. The absence of inter-raters reliability for classifying CLABSI is not totally covered by the double check of the researchers. However, the possibility of misclassification seemed to be low.

A large prospective study is recommended using a standard training program for new healthcare workers as preventive measures in the care for all newborns with central venous catheters on a NICU.

Conclusions

We did not find a CLABSI reduction in UVCs despite the introduction of preventive bundles. This disappointing result may have been caused by the significant older postnatal age at insertion in the post-intervention period, the use of a new insertion tool and the large group of healthcare workers who were involved in the insertion of UVCs. Insertion of an umbilical vein catheter should only be recommended before a postnatal age of 48 hours. Also, new nurses and residents must have the opportunity to learn specialized care for this vulnerable patient group with an UVC. Therefore we recommend training programs to develop their expertise and knowledge in the insertion and care of central venous catheters including umbilical venous catheter before working with and caring for this vulnerable patient group. Reduction of CLABSI must remain an important goal of the neonatal ward with a daily evaluation of whether or not an UVC is still required.

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7

Summary and General Discussion

Summary and general discussion

In this chapter, the most important findings of the studies in this thesis are presented. Subsequently, general and methodological considerations are discussed and future perspectives are described.

Summary

The use of peripheral IV catheters or central venous catheters has become standard practice in neonatal intensive care units (NICUs). Unfortunately these venous devices are associated with complications, resulting in morbidity and occasionally mortality. Implementation of preventive measures to reduce these complications is a core responsibility of caregivers and will improve patient safety.

In Chapter 2 the effect of intermittent flushing with saline versus heparin on prolonged indwelling time in intravenous locks (IVLs) was analysed.

An IVL is used for intermittent administration of medication. For prolonged patency the IVL has to be flushed 3 times per day. The use of heparin as flush solution may prolong the patency of the IVL, but this is not without risks. Therefore, a prospective randomized controlled trial was performed comparing heparin and saline as flush solution of the IVL with patency duration as the primary outcome.
We analysed 88 IVLs: 42 IVLs were flushed with heparin and 46 IVLs were flushed with saline.

The Kaplan-Meier plot shows similar proportions of IVLs remaining patent in the saline and heparin groups at times up to 400 hours. No statistically significant difference was found in patency between the 2 groups (log rank test p=0.27).

Therefore, we propose that saline is preferable above heparin as a flush solution. The risk in errors of preparation or administration (e.g. heparin overdose) can thus be avoided. Also, the risk of heparin induced thrombocytopenia and intraventricular haemorrhage will probably be diminished.

However, for prolonged use of total parenteral nutrition (TPN) or hyperosmolar solutions, a central venous catheter (CVC) is needed. Unfortunately, the use of a CVC increases the risk of complications during insertion and indwelling time of a CVC.

In *Chapter 3* our retrospective study compared the complication rates between umbilical venous catheters (UVCs) and peripherally inserted central catheters (PICCs) and the effect of different variables on complications. In total, 140 UVCs and 63 PICCs were included during a 16 months period. We observed no significant difference in percentage of catheter removals due to complications between the UVCs and the PICCs in the first 14 days (Log rank test p=0.66). Central line associated bloodstream infection (CLABSI) had the highest complication incidence in both

groups, followed by obstruction, dislocation, leakage and extravasation. When CLABSI was defined as 'overall CLABSI' (laboratory-confirmed CLABSI and Clinical Sepsis (CSEP)) we found an incidence of 15% in UVCs and 19% in PICCs. When only laboratory-confirmed CLABSI was used as definition, we found an incidence of 4.3% in UVCs and 11.1% in PICCs. There was no statistically difference in the incidence of CLABSI between UVCs and PICCs.

UVCs were assumed to carry an increased risk on CLABSI because of the increased colonization of the umbilical stump. This was the reason for the removal of UVCs around day 7. Remarkably, in our study, PICCs had a higher CLABSI rate when compared to UVCs. The use of an UVC seemed to be relatively safe until day 14 in comparison with the use of PICCs. This is in agreement with earlier studies (1,2). Nevertheless, the policy in each NICU should always be to remove the CVC when possible in order to reduce the risk of CVC complications.

The results gave us insight into the complication rates in our unit. This forms a good starting point to perform more research on new interventions that can reduce CVC complications and therefore increase patient safety.

In Chapter 4, the complications of the UVCs in prone position were analysed in a pilot study. Prone position is assumed to be the best position for vulnerable neonates with respiratory problems. However, in the literature, data was not available to indicate whether prone position with an UVC was safe. The complications of 88 UVCs in newborn infants positioned for at least 12 hours of 48 consecutive hours in prone position were studied.

We observed a high incidence of local minor complications such as wet or red umbilical rim. 'Overall CLABSI' (laboratory-confirmed CLABSI and CSEP) was the most important complication resulting in removal of a catheter (18.2%, 30.2 per 1,000 catheter days). This incidence was also higher than in UVCs in supine position in the retrospective study mentioned in Chapter 3. Laboratory-confirmed CLABSI was only confirmed in 9.1% of the CLABSI removals (17.0 CLABSIs per 1,000 catheter days).

Possible explanations for this observation are the differences in methodology (retrospective versus prospective) and the size of the study population. Other complications such as obstruction, leakage and perforation were comparable between the 2 studies. An umbilical rim with pus excretion had a relative risk of 3.3 for CLABSI as compared to a clean rim. A wet umbilical rim had a relative risk of 4.0 for pus excretion when compared to a dry rim. Therefore, we conclude that observation of a wet umbilical rim should raise awareness of the high risk for pus excretion and as a consequence should end prone position care. An UVC needs to be removed when pus excretion is observed. Nevertheless, an indwelling UVC should not be considered as a contra indication for prone positioning.

In Chapter 5, the effect of introducing of preventive bundles to decrease the CLABSI incidence in PICCs inserted using the modified Seldinger technique was

described. It is well known that preventive bundles reduce CLABSI in PICCs, inserted using the traditional insertion technique. The differences in insertion technique between those 2 techniques, such as multiple steps in the insertion procedure, longer duration of the procedure and risk of blood vessel perforation by the guide wire using the modified Seldinger technique, may affect CLABSI outcome (3). Forty-five newborn infants with PICCS were enrolled in this study before the introduction of bundles of preventive measures and 88 newborn infants were enrolled after the introduction. Preventive bundles consisted of sharing analysis and results of the post-intervention period with the whole NICU team, introduction of an insertion checklist, adapting existing protocols to the most recent evidence based developments and a standard daily assessment whether or not the catheter was still needed. Laboratory-confirmed CLABSI decreased from 12.9 per 1,000 days (13.3%) to 4.7/1,000 days (4.5%, p=0.09). When using a survival analysis, the overall CLABSI rate (laboratory-confirmed CLABSI and CSEP) reduced significantly after introduction of bundles (Kaplan-Meier survival analysis p= 0.02). There were no other variables that affected outcome.

The reduction observed in this study is comparable with that in the literature when using the traditional insertion technique. Therefore, preventive bundles with a minimum of costs are also successful in PICCs inserted using the modified Seldinger method.

In Chapter 6, the effect of preventive bundles to decrease the CLABSI incidence in UVCs was described. We enrolled 72 newborn infants with UVCs in the pre-intervention period. After the introduction of preventive bundles (consisting of a new insertion tool, sharing analysis and results with the whole NICU team, introduction of an insertion checklist, adapting existing protocols to the most recent evidence based recommendations and standard daily assessment of whether or not the catheter was still needed) 149 newborn infants with UVCs were included.

CLABSI was the most important complication that resulted in removal. In the pre-intervention period the laboratory-confirmed CLABSI rate was 10.0 per 1,000 catheter days (6.9%) versus 10.8 per 1,000 catheter days in the post-intervention period (7.4%, p=1.0). In the pre-intervention period the overall CLABSI rate (laboratory-confirmed CLABSI and CSEP) was 18.0 per 1,000 catheter days (12.5%). After introducing preventive bundles, we found an incidence of 26.4/1,000 catheter days (18.1%, p=0.36). When using the Kaplan-Meier survival plot with the overall CLABSI and the laboratory-confirmed CLABSI as event, we did not find a significant difference between the pre- and the post-intervention period (respectively p=0.12, p=0.61).

One of the explanations for this observation is the fact that the team who inserted UVCs is larger than the team who inserted PICCs. Also, it is important to note that the residents were frequently changed from our unit during this study.

Second, the change in insertion tools (a non-disposable insertion tool delivered by our hospital sterilization department was changed to an all-in-one disposable

tool) for umbilical catheters during the study of preventive bundles, may have influenced the outcome. In practice, the insertion pincet of the new system was not as well manufactured as the one we used before. This may have prolonged insertion time and probably increased the frequency of manipulation to the stump. Another factor may have been that in 6% of the post-intervention population an UVC was inserted after a postnatal age of 48 hours. We concluded, based on our study data, that postnatal age at time of UVC insertion did indeed influence outcome.

In summary, insertion at a postnatal age > 48 hours, less well trained inserters and the change in insertion tools, may have influenced the outcome in the post-intervention period resulting in an equal CLABSI incidence as compared to the pre-intervention period. We recommend that UVCs not be inserted after 48 hours and that adequate training be provided to residents before participation in UVC insertion for a newborn.

General discussion

The papers in this thesis provide an overview of intravenous catheter complications and the impact on health care for newborn infants. In this chapter we will present and discuss our data.

In Table 1 and 2, all baseline characteristics and reasons for removal are illustrated for UVCs and PICCs separately.

Complications of IV catheters in newborns

In approximately 20% of all CVC studies, non-elective removal (removal because of complications) occurred (Figure 1).

Prevention of these complications should be an important goal. Obstruction, dislocation and leakage are relatively low in CVCs, when compared to IVLs. This is to be expected because in IVLs the cannula is inserted for no more than 3 centimetres into the vein as compared to CVCs, which have a higher dislocation and leakage risk.

Figure 1 Complication incidence of central venous catheters in all studies

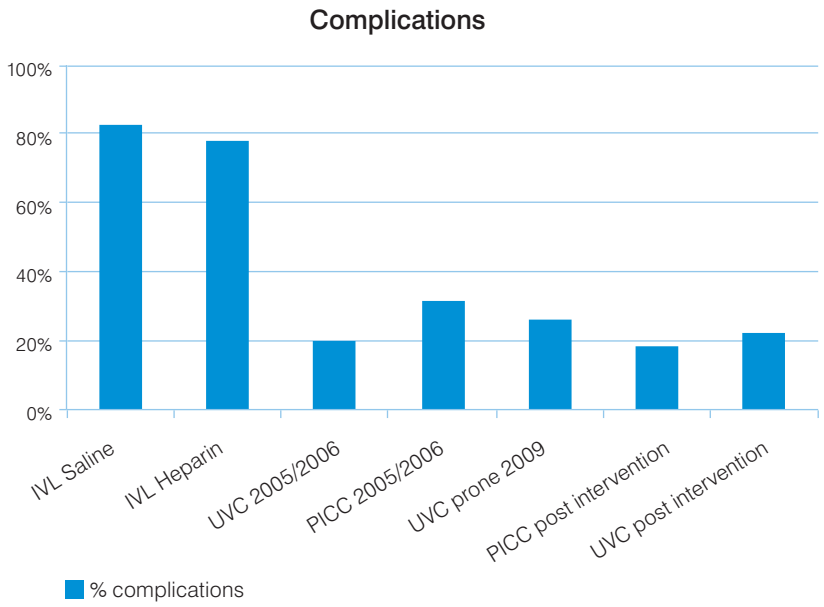


Table 1 Overview of the UVC studies

	UVC n=140 2005-2006 retrospective Chapter 3	UVC n = 88 09-2009 09-2010 Chapter 4	UVC n=72 10-2009 04-2010 Pre-intervention Chapter 6	UVC n=149 01-2011 12-2011 Post-intervention Chapter 6
Birth weight in grams mean ±SD	1986 ±1118	1345 ±665	1808 ±972	1886 ±1057
Gestational age in weeks mean ±SD	33.2 ± 5.0	29.7 ± 3.0	31.4 ± 4.7	32.1 ± 5.0
Catheter duration in days mean ±SD	6.9 ± 2.7	6.0 ± 2.8	6.9 ± 3.3	6.8 ± 3.6
Elective removal	79 (56.4)	51 (58.0)	39 (54.1)	92 (61.8)
Death/Transfer	33 (23.5)	0	18 (25.0)	27 (18.0)
CLABSI	21 (15.0)	16 (18.2)	9 (12.5)	27 (18.1)
CDC CLABSI	6 (4.3)	8 (9.1)	5 (6.9)	11 (7.4)
Clinical Sepsis	15 (10.7)	8 (9.1)	4 (5.5)	16 (10.7)
Obstruction	0	1 (1.1)	0	0
Dislocation	4 (2.9)	5 (5.7)	5 (6.9)	4 (2.7)
Leakage	3 (2.1)	1 (1.1)	1 (1.4)	0
Extravasation, perforation	0	0	0	0

Values are numbers (%) unless otherwise is mentioned.

When comparing the less common complications as obstruction, dislocation and leakage between the UVCs during the years, we can conclude that this remains stable (Figure 1). Dislocation was the most frequent reason for removal, followed by leakage. Obstruction of the UVC was rare.

When comparing these less common complications in PICCs during the years, we observe the same finding (Table 2). However, in the pre-intervention group, none of these complications were found. The obstruction risk might be slightly higher in PICCs. On the other site, dislocation was rare in the PICCs and slightly higher in UVCs. A possible explanation is the fact that the fixation of the UVC in the umbilical rim is more difficult because the umbilical stump dries up during the days. This makes fixation less tight when comparing to the fixation of the PICC with adhesive dressing on the skin.

We can conclude that these complications are rare in UVCs and PICCs. For this reason it is understandable that we could not find more literature about these less common complications in CVCs. However, we think it is important to have knowledge

Table 2 Overview of the PICC studies

	PICCs n=63 2005-2006 Retrospective Chapter 3	PICCs n=45 10-2009 04-2010 Pre-intervention Chapter 5	PICCs n=88 01-2011 12-2011 Post-intervention Chapter 5
Birth weight in grams mean ±SD	1530 ± 937	1460 ± 796	1787 ±1053
Gestational age in weeks mean ±SD	30.6 ±4.4	30.7 ± 4.3	32.1 ± 4.9
Catheter duration in days mean ±SD	10.2 ± 5.2	10.3 ± 5.5	9.9 ±6.2
End of treatment	24 (38.1)	22 (49.9)	41 (46.6)
Death/Transfer	19 (30.2)	9 (20.0)	31 (35.2)
CLABSI	12 (19.0)	14 (31.1)	10 (11.5)
CDC CLABSI (Criteria 1 and 2)	7 (11.1)	6 (13.3)	4 (4.5)
Clinical Sepsis (Criterion 3)	5 (7.9)	8 (17.8)	6 (6.8)
Obstruction	5 (7.9)	0	1 (1.1)
Dislocation	0	0	2 (2.3)
Leakage	1 (1.6)	0	2 (2.3)
Extravasation perforation	2 (3.2)	0	0
Others	0	0	1 (1.1)

Values are numbers (%) unless otherwise is mentioned.

about the incidence of these less common complications, even though these are hard to prevent. Improvement of the UVC fixation, which results in longer UVC indwelling time, will increase patient safety.

As we showed in the overview, CLABSI is a more common and more serious complication, which might be preventable. Diminishing this complication has favourable influence on patient safety and health care costs. So this makes the focus in the literature valuable.

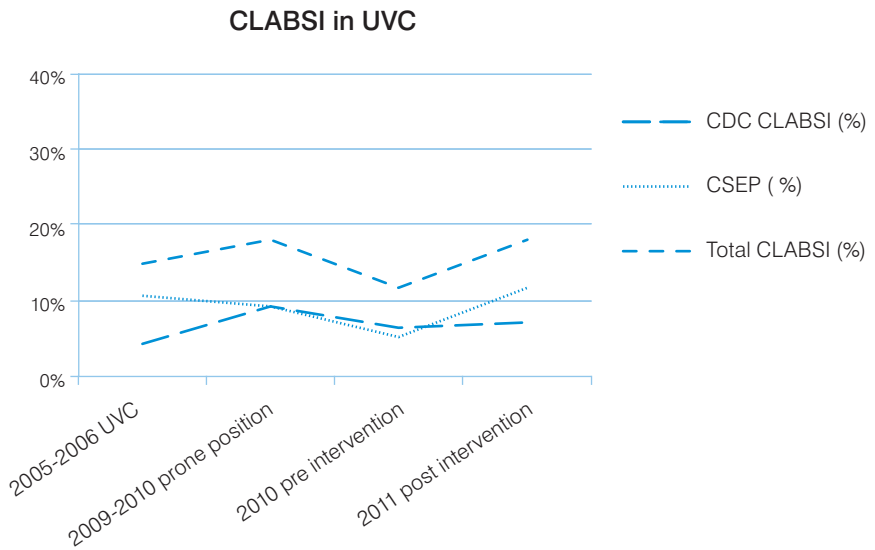
CLABSI may also occur in peripheral IV catheters but it is not common because of the shorter indwelling time of the catheter and the peripheral position of the cannula. In figure 2 and 3, the CLABSI incidence of all the CVC studies are illustrated with a range of overall CLABSI between 11.4% and 31.1% during the 6 year period.

The more recent studies were prospective observational studies and identification of CLABSI is probably more reliable than in the retrospective study. When analysing the highest incidence of overall CLABSI in PICCs and in UVCs (for PICCs the pre-intervention group and for UVCs the prone position group) we conclude that in both groups the newborn infants had the lowest birth weight and gestational age. Although birth weight did not influence the outcome in these 2 studies, in this overview between all the studies, it is more or less remarkable. However, this is not surprising as several studies show that low birth weight increases the CLABSI risk (4,5).

An explanation for the lower birth weight in the prone position may be the reason that premature infants need more respiratory support than term infants and for this reason were placed in prone position earlier.

We expected to observe a decrease of CLABSI after introduction of the new material and bundles in the UVC study, however, we did not find a significant difference. So the introduction of the new material may have affected the outcome. Another important factor may be the fact that residents inserted UVCs. Residents rotate every 3 to 12 months, in contrast to neonatologists and nurse practitioners who are permanent members of the team. So most residents were not involved from the beginning of this study, which may have influenced their awareness that CLABSI is a preventable complication. Also, the postnatal age at insertion was an important issue that may have affected the outcome.

Figure 2 CLABSI incidence in UVC during the years in all the studies

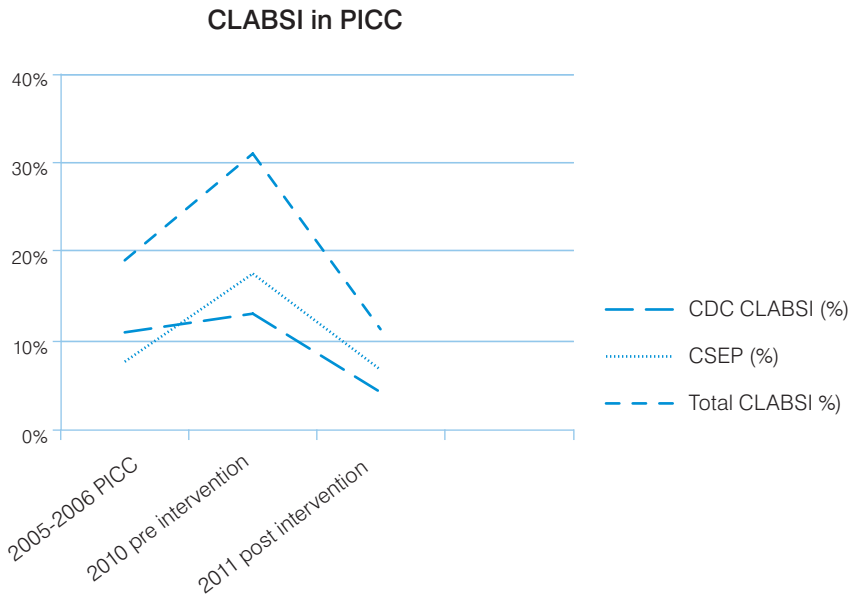


When analysing CLABSI incidence in PICCs during the last years, we observed a remarkable decline of CLABSI in the post-intervention period in 2011 when compared to the pre-intervention period of 2010 (Figure 3). We found this decline too, although less impressive, when we compared the results of the retrospective study with the post-intervention period.

During the intervention period, the material for IV catheters did not change. Also only neonatologists inserted PICCs. This team was highly trained and did not change during the latest study, unlike the UVC analysis.

This raises an important issue. Golombek et al. described a decrease of CLABSI from 15.8 to 5.1 per 1,000 catheter days after implementation by a PICC maintenance team (6). Taylor et al. also mentioned that the implementation of a specialized team might improve the care in insertion and maintenance of CVCs (4).

Figure 3 CLABSI incidence in PICCs during the years in all the studies



In chapter 5, we hypothesized that awareness of CVC related complications increases the responsibility of the caregiver to prevent these complications. However, it was also shown in chapter 6 that changing the team or the material may diminish this positive influence. Therefore, it is important to provide continuous training for the whole NICU team with special focus on new residents and nurses who take care of newborn infants with IV devices.

Several other factors may also influence complication rates such as the definition of CLABSI, patient characteristics, underlying illness, use of antibiotics, etc.

Definition of CLABSI

The definition of CLABSI has been changed. The Center for Disease Control and Prevention (CDC) changed their definition during the years of our study. In 2002, they defined CLABSI as any bloodstream infection that occured while a CVC was in place and up to 48 hours after its removal (2002). In January 2008 the CDC modified this CLABSI definition. One positive blood culture yielding a normal skin contaminant did not fulfil the definition anymore (1). Horan et al. described CLABSI as a laboratory-confirmed bloodstream infection with a catheter in place for a minimum of 2 days or in place on the day of event or the day before (7). Laboratory-confirmed bloodstream infection was defined by using one of the first 2 following definitions: Criterion 1 was defined as 1 or more positive blood cultures, with the exception of skin micro-organisms, not related to another infection source. Criterion 2 was defined as clinical signs of sepsis (especially for patients $<$ 1 year old), such as fever or hypothermia, apnoea or bradycardia, and 2 or more positive blood cultures drawn on separate occasions with the same micro-organism (including skin micro-organisms) and no other infection source. The criterion had to be satisfied within a timeframe that did not exceed a gap of 1 day. This definition of laboratory-confirmed CLABSI is the most pure definition (1,8).

Schulman et al. proposed that the change of the CLABSI definition resulted in a significant CLABSI decline (65%) in newborn infants (9). We agree with Taylor et al. that the laboratory-confirmed CLABSI rate underestimates the actual rate because it is almost impossible to obtain 2 blood cultures in newborn infants (4).

Unfortunately, different definitions of CLABSI are used in the literature, thus complicating a comparison between different studies. Some studies follow the CDC criteria and have a low CLABSI incidence (9,10) while other studies use their own definitions and include clinical CLABSI too (11,12).

Using only the definition of laboratory-confirmed CLABSI excludes newborns treated with antibiotics because of clinical signs and/or laboratory signs of sepsis with only an indwelling CVC. Due to the difficulty to acquire a reliable blood volume for a culture, it can be possible that there is no positive blood culture or only 1 culture with a skin micro-organism. The presence of a blood culture with only a skin micro-organism can be explained by contamination from the sample taken from the skin of the newborn or healthcare personnel (13).

Horan et al. reported that Clinical CLABSI (CSEP) may only be used to report primary blood stream infections in neonates and infants (7). This requires one of the

following signs or symptoms (fever or hypothermia, apnoea, or bradycardia) with no other recognized cause and blood culture not done or no organism detected, no apparent infection on another site and physician institutes treatment for sepsis. Our CSEP definition is adapted from this definition. To meet the CDC definition of laboratory-confirmed CLABSI in case of a skin microorganism, 2 or more cultures drawn on separate occasions are needed. In the CDC definition of CSEP a blood culture is not done or no organisms are detected in blood. So, there is no definition available in situations with only 1 positive blood culture with a detected skin-micro-organism. We included these cases in our group for CSEP. Clinical CLABSI is an extensive group, as we have shown in our studies.

Ignoring CSEP will give a distorted interpretation of CLABSI incidence because this group is treated at least for 3 days with antibiotics because of clinical and/or laboratory signs. This probably results in a delayed NICU discharge, a higher morbidity and mortality risk and also increased health care costs. As we have seen in the more recent studies, the CDC CLABSI definition is followed more and more. It will be important to follow the CDC CLABSI criterion for further research to compare the outcome between the studies, however the CSEP should be registered separately.

Other factors which may influence the outcome of complications

1. Patient characteristics

Due to better-developed techniques, more very low birth weight newborns survive the NICU period. In a review of these studies, the population consists of very low birth weight newborns (500 grams) until term newborns (> 3500 grams). This is an enormous variation in (birth) weight.

The influence of birth weight on the indwelling time and complications of IV devices in newborn infants, is one of the most frequently mentioned variable in the outcome of these studies. It is reasonable to assume that small catheters usually used in preterm newborns can more easily be obstructed. The very low birth weight (VLBW) newborn needs longer TPN or medication therapy which results in longer indwelling time and thus, includes more frequent manipulations. A longer indwelling time of the catheter increases the risk of complications. A retrospective cohort study of Sengupta et al. demonstrated an increased CLABSI incidence by 14,0% per day in the first 18 days (10). From Day 36 to Day 60 the CLABSI increase was 33.0% per day.

Another option to address this variable is to stratify the results to birth weight categories. Some studies were able to divide the population into more birth weight groups. These studies showed significant differences in indwelling times of venous access or complications due to birth weight. Hanrahan et al., Mahieu et al. and Taylor

et al. mentioned that infants weighting ≤ 750 had a CLABSI rate of 2.5/1,000 catheter days, decreasing to 0.6/1,000 catheter days for infants > 1500 grams (4,5,14). Only in our last study, we found an increased CLABSI risk for low birth weight newborns. In the overview of our studies, we found a higher CLABSI rate in the 2 groups with lowest birth weight, however, we didn't find that birth weight influenced the outcome in either study (Table 1 and 2). Further research with a larger group, divided or stratified into specific birth weight groups is recommended.

Other factors such as illness severity, individual coagulation conditions, the degree of sedation and distress or restlessness may also affect outcome. Distress can decrease the indwelling time of a venous access due to uncontrolled movements, resulting in infiltration or dislocation and thus resulting in the removal of the catheter. In addition, sedation of newborns can give a prolonged indwelling time.

2. Medication, parenteral nutrition and antibiotics

An IV access is necessary because of the administration of medication and parenteral nutrition.

It is well known that administration of medication and parenteral nutrition affects the patency.

As shown in Chapter 2, the use of sodium bicarbonate did prolong the catheter patency, although not significantly. This is not surprising because sodium bicarbonate has been used as a flush solution for catheter clearance (15). The use of TPN, especially the fat solution that premature newborns receive, is associated with increased bacteraemia by *coagulase negative Staphylococcus*. This is probably due to the longer indwelling time and an increased number of catheter manipulations (15).

It is also well known that the use of calcium in combination with other solutions may result in precipitation, which can obstruct the catheter. Although we used calcium in our TPN, we did not have a high obstruction rate in the UVCs and PICCs. However, Sha mentioned a study by Nakamura (1990), which reported a complete (33%) and partial (33%) occlusion in catheter tips after electron microscopic examinations (16).

Endothelial damage during catheter placement, blood vessel occlusion, low infusion rates, patient and infusate characteristics, such as TPN and fat solutions are factors that have been associated with thrombosis. Thrombosis is associated with an increased CLABSI risk. In our studies, we did not analyse all the medications and solutions given through the catheters but propose that this may influence the complication rates.

The use of heparin versus saline on the catheter indwelling time was only studied in the IVLs. In our NICU, we still continue the use of heparin in PICCs and UVCs because of the reduced risk of catheter occlusion (16).

Antibiotics are prescribed when clinical signs appear in the first days after birth, or in case of infections such as pneumonia or necrotising enterocolitis. It is well known

that the use of antibiotics result in changes in the gastrointestinal microbiome. The microbial ecosystem has an important role in the protection against pathogenic micro-organisms. Changes in microbiome due to antibiotic use may influence the risk of infection and increase the occurrence of (nosocomial) infections and/or CLABSI (17).

Recommendations to decrease complications

Quality improvement programs, including preventive bundles, have resulted in reduction of CLABSI in several studies. However, there is a wide variation in the type of bundles.

Many studies show a reduction in CLABSI when using dedicated teams, participating in a national transparent survey system, or participating in a CLABSI-reducing-bundles-research project (9,18,19). Most bundles include a mixture of strategies.

Improvements in maximum sterile barrier precaution, hand hygiene standards, dedicated team, checklists, hub disinfection and a closed medication system, all reduce the rate of CLABSI. It is difficult to define specific interventions that make the most difference.

In our study, we showed the effect of simple bundles to prevent CLABSI with a minimum of costs. However, we found a deterioration of CLABSI incidence when it was combined with the introduction of a new UVC insertion tool. Therefore, we conclude that introduction of new equipment may have affected the outcome. A second cause could be the rotation of residents on a NICU, specifically the difference in experience in the insertion procedure. Although these components probably affected the CLABSI rate in the UVC study, the most important reason for CLABSI reduction must be, in our opinion, increased awareness of the healthcare team of the importance of prevention of catheter related complications by sharing the results and education.

Taylor et al. found a common thread in several bundles in the literature. Standardization in clinical practice, support for the interventions, education of the caregivers and neonatal staff engagement were important issues making a reduction of CLABSI more successful. It is not which intervention bundle is most successful, but how the bundles are implemented and how they are controlled (4).

Structural education of the caregivers (neonatologists, residents and nurses) is essential to develop or increase the caregiver's knowledge of problems with all vascular devices. In our NICU, nurses have a theoretical examination every 3 years, followed by clinical training. However, new personnel do not usually have the practical skills or undergo a theoretical examination before they become involved in the care for newborn infants. For example, new residents start with inserting the umbilical catheter as part of training on the job. It is recommended that a training in skills lab to develop practical skills in the insertion and maintenance of vascular devices be completed by residents before working in the NICU.

Future Considerations

When intravenous therapy is necessary, a peripherally intravenous device or an IVL will give less severe complications and is the first option. When a CVC is necessary, an UVC need to be inserted before the age of 48 hours and does not exceed an indwelling time of a maximum 14 days. Removal of the CVC must be a daily consideration. The care for a newborn with an indwelling umbilical catheter in prone position is possible with the advices which were given. Simple bundles as described must be a standard care. Structural training programs and sharing complication outcomes of the intravenous devices with the neonatal caregivers are important. We recommend that new neonatal caregivers (nurses, residents and medical staff) pass an e-learning theoretical examination and a practical skills test before working with newborn infants with intravenous devices.

Creating a Dutch national CLABSI survey which gives insight into hospital programs and CLABSI rates will increase health caregiver's awareness as well. This will also create more discussion and learning opportunities between NICUs with only one goal: improvement of catheter care for newborn infants.

Further research should be focused on the effect of various preventive measures in the incidence of CLABSI and other complications of intravenous devices in newborn infants, such as:

- The effect of antimicrobial-coated catheter on the CLABSI incidence.
- The effect of prior training in skills lab on the incidence of catheter complications.
- The development of better preventive bundles and the investigation of results in the reduction of catheter related complications.
- The influence of gestational age, birth weight, postnatal age at insertion on the incidence of CLABSI and other catheter-related complications.

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8

Samenvatting | Dutch summary

Samenvatting | Dutch summary

De laatste 30 jaren is de overlevingskans van zieke pasgeborenen en te vroeg geborenen op een neonatale intensive care unit (NICU) enorm toegenomen door de ontwikkeling in kennis en kunde op neonataal gebied. De behandelingen van deze patiënten zijn door de jaren heen ook complexer geworden. Deze complexiteit vergroot de kans op een toename van complicaties waarbij voortdurend de afweging gemaakt dient te worden hoe de patiëntveiligheid het beste geborgd kan worden.

Bij vrijwel elke zieke pasgeborene (geboren vanaf 24-42 zwangerschapsweken) is een intraveneuze toegang nodig voor het toedienen van medicatie of voeding. Echter, het gebruik van een perifeer infuuscanule en van een centraal veneuze catheter is niet zonder risico's. Minder ernstige tot ernstige complicaties kunnen optreden met als gevolg een langere opnameduur, extra kosten en soms zelfs overlijden.

Zo bestaat bij het gebruik van een perifeer infuuscanule een risico op extravasatie, obstructie en phlebitis tot infectie door de vaak meerdere pogingen die nodig zijn om een perifeer infuus in te brengen (gemiddeld 2,2 pogingen). Het blijkt dat een infuus vaak na 1 tot 1,5 dag vervangen moet worden omdat het niet meer voldoende functioneert. Het zou wenselijk zijn om een perifeer infuus te hebben dat zo lang mogelijk goed toegankelijk is.

Wanneer dat mogelijk is, wordt een perifere canule doorgespoten met fysiologisch zout of een heparine oplossing en vervolgens afgesloten met een dopje en alleen gebruikt voor intermitterende medicatie of vloeistoffen. Het wordt aanbevolen om bepaalde vloeistoffen en/of medicatie niet over een perifeer infuus te laten lopen in verband met viscositeit, met als gevolg een snelle obstructie van de infuuscanule. Een ander voorbeeld is het toedienen van medicatie met een lage zuurgraad. Het wordt aanbevolen dit niet toe te dienen via een perifeer infuus aangezien dat schadelijk is voor het bloedvat en pijnlijk is voor de patiënt. In deze situaties, en bij langdurig totaal parenterale voeding, wordt besloten tot het inbrengen van een centraal veneuze catheter (CVC) in één van de grote bloedvaten. Bij een pasgeborene kan een CVC in de eerste dagen ingebracht worden in de navelvene. Wanneer een navelvene niet meer toegankelijk is wordt gekozen voor een groter perifeer bloedvat waarin een catheter wordt opgeschoven tot aan de overgang van het rechter atrium. Echter, ook een CVC kan complicaties geven zoals obstructie van de lijn, thrombose, lekkage van de catheter of de insteekopening of centrale lijn geassocieerde bloedinfectie (CLABSI).

Derhalve is het belangrijk om goed in kaart te brengen wat de bijzonderheden zijn rondom de verschillende infuustoegangen, zodat een infuustherapie gekozen kan worden voor de pasgeborene met het minste risico op complicaties.

In Hoofdstuk 2 stond het perifeer infuus slotje centraal. Dit is een infuuscanule welke met een dopje is afgesloten nadat het is doorgespoten met een heparine oplossing

(anticoagulantia) om hiermee de obstructie van de infuuscanule te voorkomen. Heparine is een anticoagulantium dat in hoge dosis bij vroeg geboren kinderen heparine induced trombopenia en hersenbloeding kan geven. Aangezien heparine in het algemeen in een zeer lage dosering werd toegediend, werd het gebruik van heparine op de NICU reeds lang geaccepteerd. Echter in studies bij volwassen patiënten is gebleken dat een perifeer infuus slotje net zo lang doorgankelijk bleef na het doorspuiten met fysiologisch zout in vergelijking met een heparine oplossing. Deze resultaten konden echter niet zomaar geëxtrapoleerd worden naar de te vroeg geborenen. In een prospectief gerandomiseerde studie werden 46 infuus slotjes doorgespoten met fysiologisch zout en vergeleken met 42 infuus slotjes doorgespoten met een heparine oplossing. De primaire uitkomstmaat van deze studie was het (zo lang mogelijk) doorgankelijk houden van een infuuscanule. Immers, een langere doorgankelijkheid van een infuuscanule voorkomt meerdere prikpogingen en biedt meer continuïteit in de medicatie toediening. In deze studie werd geen verschil in doorgankelijkheid gevonden tussen de infuuscanules doorgespoten met heparine of met fysiologisch zout (p=0,27). Aangezien het gebruik van heparine tot meerdere complicaties kan leiden en doordat het verdunnen van deze oplossing ook tot medicatiefouten kan leiden, is het gebruik van fysiologisch zout aan te bevelen in het doorspuiten van infuuscanules bij neonaten.

In Hoofdstuk 3 werd op retrospectieve wijze de complicatie incidentie van de navelvene catheter en perifeer ingebrachte centrale catheter (PICC) vergeleken. Er werden 140 pasgeborenen met navelvene catheters en 63 pasgeboren met PICC's onderzocht.

Opvallend was dat in 49,7% van de navelvene catheters de catheter na 7 dagen nog in situ was. Dit in tegenstelling tot het advies in het bestaande protocol om een navelvene catheter rondom dag 7 te verwijderen. De meest voorkomende complicatie waardoor een CVC verwijderd werd was CLABSI, gevolgd door obstructie, dislocatie, lekkage en extravasatie van een catheter. Hoewel aangenomen werd dat navelvene catheters een hogere kans op CLABSI zouden hebben gezien de hoge graad van bacteriële kolonisatie bij necrose van de navelstomp in vergelijking met PICC's, bleek in onze studie het tegendeel. In de navelvene catheter groep was er in 15,0% sprake van CLABSI (laboratorium bevestigde CLABSI 4,3%) en in de PICC groep was dit 19,0% (laboratorium bevestigde CLABSI 11,1%). In deze studie zagen we geen significant verschil tussen het verwijderen van een navelvene catheter en een PICC ten gevolge van een complicatie in de eerste 14 dagen dat een catheter in situ was (p=0.66). Derhalve kunnen we concluderen dat het in situ blijven van een navelvene gedurende 14 dagen relatief veilig is. Desondanks blijft onze aanbeveling te allen tijde een CVC te verwijderen wanneer ook maar enigszins mogelijk is, om de kans op complicaties te vermijden.

In Hoofdstuk 4 werd in een pilot studie de incidentie van complicaties bij navelvene catheters wanneer een pasgeborene in buikligging verzorgd werd,

onderzocht. Buikligging bij de te vroeg geborenen (aan monitorbewaking) is een betere ligging gebleken voor de ademhaling. Echter de observatie van de navelvene lijn wordt op deze wijze bemoeilijkt. Eveneens werd aangenomen dat er door buikligging een toename zou zijn van complicaties, gerelateerd aan de navelvene catheter. In meerdere NICU's in Nederland was het toegestaan om pasgeborenen met een navelvene catheter in buikligging te verzorgen in verband met het positieve effect op de ademhaling. In de literatuur vonden we hierover geen aanbeveling. Echter gezien het belangrijke effect op de ademhaling werd besloten conform de andere NICU's in Nederland ook buikligging toe te staan bij pasgeborenen met navelvene catheters in situ. Tegelijkertijd werden de complicaties geregistreerd. In dit onderzoek werden 88 pasgeborenen met een navelvene catheter geïncludeerd. Een minimale buikliggingsduur van 12 uren (driemaal 4 uren achter elkaar) in 48 uren was een vereiste. In dit onderzoek zagen we een hoge incidentie van lokale minder ernstige complicaties zoals roodheid van de navel tot natte navel. Opnieuw was CLABSI de belangrijkste oorzaak bij de niet-electieve redenen om een navelvene catheter te verwijderen (18,2%, laboratorium bevestigde CLABSI 9,1%). Wanneer er sprake was van een natte navel, bleek er een 4,4 keer zo grote kans te zijn om een pussende navel te ontwikkelen. Wanneer er sprake was van pus rondom de navel dan was het risico op CLABSI 3,3 keer hoger.

Door het ontbreken van een goede vergelijking (gerandomiseerd onderzoek) kunnen we niet concluderen dat de lokale complicaties toegenomen zijn. Aangezien de ernstige complicaties vergelijkbaar zijn met hetgeen in de literatuur gemeld wordt, concluderen we dat een pasgeborene met een navelvene catheter in situ wel in buikligging mag liggen mits de navel niet nat is. Bij aanwezigheid van pus dient de navelvene catheter altijd direct verwijderd te worden.

In Hoofdstuk 5 werd het effect van preventieve bundels (verscherpte handhygiëne, insertie checklist, aanpassen van protocol naar recentste richtlijnen) op het verminderen van CLABSI in de PICC lijnen op onze NICU onderzocht. In de literatuur en in veel andere NICU's wordt de traditionele inbrengtechniek gebruikt waarbij een infuus geprikt wordt en een catheter door de infuusnaald zover mogelijk in het bloedvat opgeschoven wordt. Op onze NICU worden alle PICC's ingebracht conform de Seldinger techniek. De Seldinger techniek gebruikt een voerdraad om de catheter te geleiden met als doel de tip van de catheter op de meest geschikte centrale plaats te krijgen. Deze techniek vereist meer stappen bij het inbrengen, waardoor er mogelijk een wat langere inbrengtijd is in vergelijking met een traditionele catheter. Tevens vereist dit enige expertise van de inbrenger (neonatoloog). Mogelijk dat deze stappen het effect van de preventieve bundels op het verminderen van CLABSI zoals beschreven wordt bij de traditionele techniek, negatief zouden kunnen beïnvloeden. In de pre-interventie periode werden 45 pasgeborenen met PICC's geïncludeerd. In de post-interventie periode werden 88 pasgeborenen met PICC's geïncludeerd.

De laboratorium bevestigde CLABSI incidentie in de pre-interventie groep was 13,3% (12,9 CLABSI per 1000 catheter dagen) versus 4,5% (4,7 CLABSI per 1000 catheter dagen) in de post-interventie groep. Ondanks dit verschil toonde de survival analyse geen significant verschil aan tussen beide groepen (p=0.15).

Er werd wel een significant verschil gevonden wanneer gekeken werd naar de totale CLABSI incidentie (laboratorium bevestigde CLABSI en klinische sepsis) in de pre-interventie periode (31,1%, 30,2 CLABSI per 1000 catheter dagen) versus de post-interventie periode (11,5%, 11,6 CLABSI per 1000 catheter dagen) welke eveneens werd aangetoond door middel van een survival analyse (p=0.02). Deze reductie is vergelijkbaar met die van de traditionele techniek.

Daarmee kan geconcludeerd worden dat het gebruik van de Seldinger techniek voor het inbrengen van PICC's de CLABSI reductie na het invoeren van de preventieve bundels niet nadelig beïnvloedt.

In Hoofdstuk 6 hebben we eveneens onderzocht of door introductie van reeds beschreven preventieve bundels de CLABSI incidentie bij navelvene catheters werd verminderd op onze NICU. Tevens werd tegelijkertijd een disposable insertie set geïntroduceerd. Een navelvene catheter wordt door een grotere groep zorgverleners ingebracht in vergelijking met de PICC's. Arts-assistenten (roulerend in 3 tot 12 maanden), verpleegkundig specialisten en neonatologen verrichten deze handeling. In deze studie werden in de pre-interventie periode 72 pasgeborenen met navelvene catheters onderzocht, gevolgd door 149 pasgeborenen met navelvene catheters na de introductie van de preventieve bundels en de nieuwe disposable insertie set.

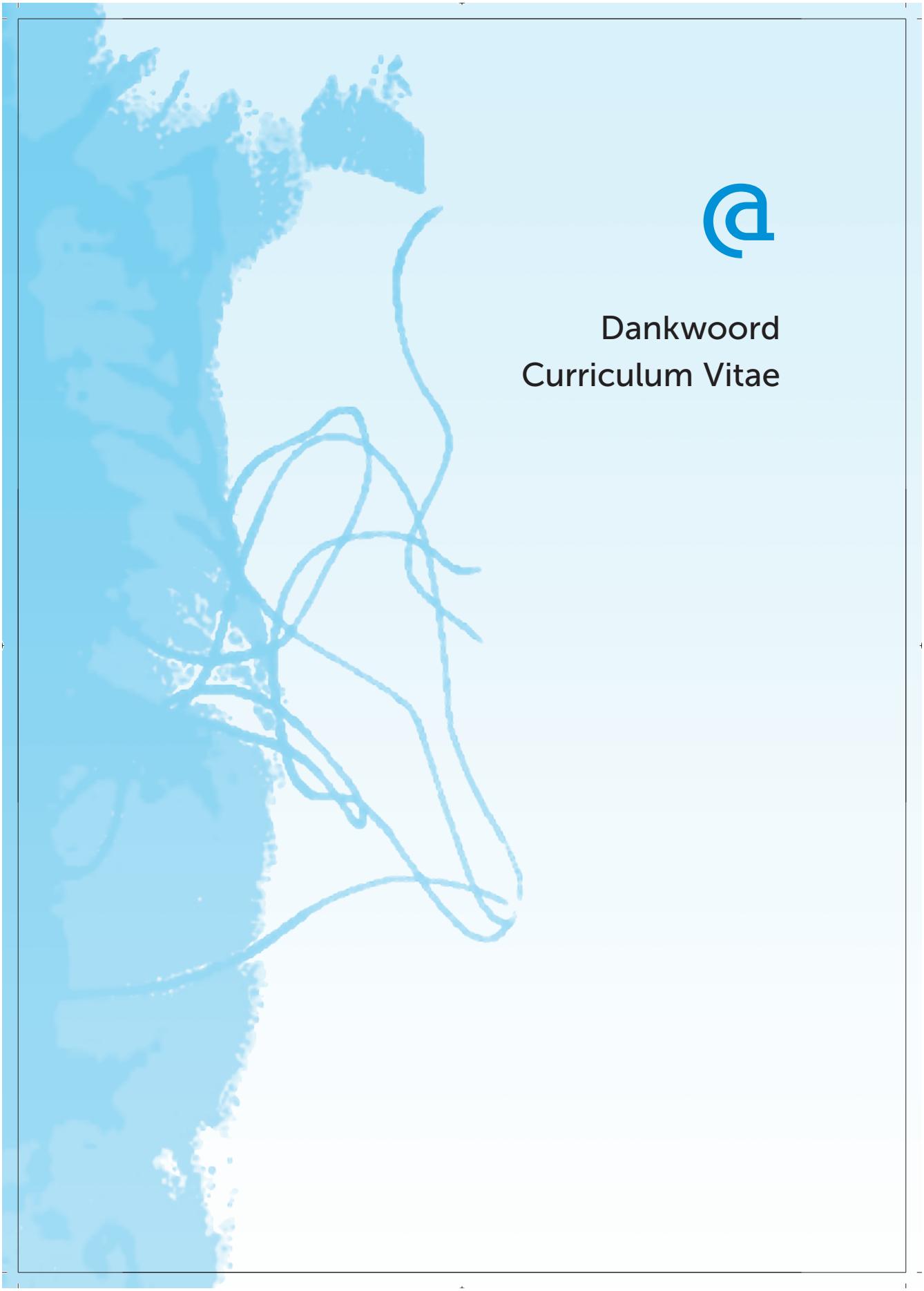
Opvallend genoeg bleek er geen reductie van CLABSI te zijn in dit onderzoek. In de pre-interventie periode was er sprake van laboratorium bevestigde CLABSI incidentie van 6,9% (10,0 per 1.000 catheter dagen) versus 7,4% in de post-interventie periode (10,8 per 1.000 catheter dagen). De survival analyse toonde geen significant verschil aan (p=0.61). Wanneer wederom gekeken werd naar de totale CLABSI incidentie (laboratorium bevestigde CLABSI en klinische sepsis) werd eveneens geen significantie aangetoond door middel van de survival analyse (p=0.12).

Een mogelijke oorzaak hiervoor is de grote groep mensen die de navelvene catheter inbrengen met verschil in expertise, gecombineerd met het veranderen van materiaal wat mogelijk tot een langere inbrengtijd heeft geleid. De postnatale leeftijd bij het inbrengen van een navelvene catheter welke in de post-interventie groep hoger was, kan eveneens de uitkomst van dit onderzoek negatief beïnvloeden. Dit kan mede een daling in CLABSI voorkomen hebben. Het inbrengen van een navelvene catheter in alleen de eerste 48 uur en inbrengen van een UVC door ervaren mensen zou een positieve bijdrage kunnen leveren aan het verminderen van CLABSI. Specifieke trainingen in het inbrengen van de catheter en het zorgdragen voor pasgeborenen met een navelvene catheter voor nieuwe artsen en verpleegkundigen is aan te bevelen.

Wanneer we de uitkomsten van de studies vergelijken zien we wisselende resultaten.

Er zijn veel factoren die een complicatie als CLABSI kunnen beïnvloeden zoals bijvoorbeeld geboortegewicht, ernst van ziekte, verschillende medicatie of antibiotica behandelingen, kennis, expertise, betrokkenheid en bewustwording van zorgverlener. Wanneer een pasgeborene een intraveneuze toegang nodig heeft, geeft een perifeer infuuscanule de minst ernstige complicaties. Wanneer een CVC nodig blijkt, adviseren we een navelvene catheter tot uiterlijk de 2e levensdag in te brengen. Deze zou tot maximaal 14 dagen in situ mogen blijven. Ook mag een pasgeborene met navelvene catheter in buikligging verzorgd worden met de reeds beschreven adviezen. Echter bij elke infuuscanule of catheter dient iedere dag overwogen te worden of deze nog noodzakelijk is, om zo onnodige risico's te voorkomen. We adviseren om de preventieve bundels dagelijks te gebruiken en waar nodig verder aan te passen.

Training van personeel, continue terugkoppeling naar zorgverleners over de stand van zaken om zo de betrokkenheid te vergroten en bijvoorbeeld een speciaal infuusteam, kan de kwaliteit van zorg en patiëntveiligheid voor patiënten met een infuus vergroten.



Dankwoord
Curriculum Vitae

Dankwoord

Het is zover! Het boek is klaar!
Hoe kan ik dit proces het beste beschrijven. Het eerste wat in mij op komt, is het benoemen van de verschillende emoties die voorbij zijn gekomen.
Verwondering: over het feit dat mij dit overkomt.
Boosheid: wanneer het zo oneindig lang lijkt te duren eer je iets terug krijgt van een tijdschrift.
Blijdschap: wanneer het artikel geaccepteerd is.
Melancholie: waar blijft de tijd dat ik weer gewoon van mijn 'vrije tijd' kan gaan genieten.
Spanning: bij de (poster)presentaties op (inter)nationale symposia.
Frustratie: wanneer mijn zo zorgvuldig geformuleerde zinnen geschrapt werden.
Trots: nu alles zover is en ik dit proefschrift aan u mag overhandigen. Eindelijk!
En dit heb ik te danken aan veel mensen. Waar zal ik dit dankwoord beginnen en waar moet ik eindigen zonder ook maar iemand tekort te doen? Ik ga mijn best doen….

Om te beginnen bij mijn (co) promotoren.
Prof. dr. de Groot, beste Ronald,
Mijn eerste echte kennismaking met je was rondom 2006. Het onderzoek met de 'heparineslotjes' was afgerond en al pratende met mijn collega verpleegkundig specialisten van kindergeneeskunde kwamen we tot de conclusie dat we de resultaten ook moesten gaan gebruiken op de andere kinderafdelingen. Samen met Karen Kwak heb ik een voorstel uitgewerkt en een afspraak bij je gemaakt (toen was je nog werkzaam als Hoofd Kindergeneeskunde). Enigszins nerveus vertelden wij ons verhaal. Op je herkenbare manier taxeerde je ons voorstel, verbeterde onze taalfouten, maar vervolgens stond je volledig achter ons en complimenteerde ons met het feit dat we ons inzetten voor kwaliteit en onderzoek. Dat ik je later in mijn carrière nog zo vaak tegen zou komen, sterker nog, dat je mijn promotor zou worden, had ik toen nooit verwacht. Kenmerkend was je duidelijkheid en doortastendheid. Dat gaf me zelfvertrouwen. Iets wat ik wel nodig had in deze, voor mij, totaal onbekende wereld. Ik twijfelde of ik wel echt kon gaan promoveren. In mijn bijzijn pakte je de telefoon en stelde je mijn bezorgde vragen aan de juiste personen. Het was meteen voor eens en voor altijd duidelijk: 'ja' dus.
Ongelooflijk veel dank voor je tijd, beoordelingen, opbouwende kritiek en doortastendheid in deze jaren.

En dan Dr. K.D. Liem, beste Djien,
Zonder jou was dit nooit gebeurd. Dat is een feit. Vanaf mijn eerste jaren op de neonatologie had ik al diep respect voor de wijze waarop je op je rustige wijze werkte en in een mum van tijd een infuus of lijn inbracht. Hoe bijzonder waren de nacht-

diensten waar jij soms na gedane zaken rustig een kopje thee pakte en je aansloot bij ons, verpleegkundigen. Als je eenmaal op gang kwam met je verhalen, dan was je niet meer te remmen. Door mijn werkzaamheden in de infuuswerkgroep van de afdeling ontstond er langzaamaan een band... als ik het zo mag zeggen. De onderzoeksvragen ontstonden en het eerste research was daar. En zo ging het verder. Ook jouw onvoorwaardelijke steun en vertrouwen in de periode waarin ik de opleiding tot verpleegkundig specialist volgde en nadien op neonatologie werkte vond ik heel bijzonder. Gedurende deze jaren heb je me op wetenschappelijk niveau gevormd tot wat ik nu ben. Je hebt me gecorrigeerd, keer op keer (ja, tot vervelens toe), maar altijd zag ik uiteindelijk weer verbetering. Je hebt me geïntroduceerd in de wereld van symposia, (poster)presentaties en nominaties. Vele uren buiten werktijd hebben we de inhoud van de onderzoeken en het proefschrift besproken. Maar ook persoonlijke zaken kwamen aan bod.
Djien, enorm bedankt voor je altijd onuitputtelijke steun en voor je vertrouwen.
Ik hoop echt van harte dat we elkaar nog regelmatig zullen ontmoeten.

Paranimfen.
Lieve Herman,
Jarenlang waren we naaste collega's en hebben we vaak heel hard gewerkt, maar nog veel vaker zoveel lol gehad. Hoe relativerend is het hebben van humor in je werk en dagelijks leven. Ik kon bij jou mijn hart ophalen.
Allebei gaven we uiteindelijk een andere draai aan onze carrière. Sterker nog... jij werd mijn verpleegkundig manager. Ook dat deed je op je eigen manier. En dit was vooral aangeven dat je er was voor alle steun die ik zou willen, maar dat ik zelf de kaders moest vormen en mijn koers moest varen. Menig gesprek heb ik op je kamer gevoerd. Menig traan heb ik daar gelaten als ik vast liep. En dan altijd was er weer een of andere opmerking waarbij het je lukte dat ik lachend je kamer verliet. Niet voor niets dat ik jou graag als paranimf naast me wilde hebben.
Dank voor alles.
Lieve Lian, of te wel 'Lilian!!!' Samen zijn we in 1994 op de NICU begonnen. En het was meteen goed. Wat hebben we samen veel gedeeld! En dan heb ik het niet alleen over de zorg voor de pasgeborenen en de ouders. Oprechte belangstelling, soms confronterende vragen, soms de 'advocaat van de duivel', maar altijd begrip en vertrouwen. Als ik dit nu schrijf lijkt dit heel saai en serieus. Maar het tegendeel is een feit: lachen, lol, van alles uitspoken en jaarlijkse weekendjes weg. Met jou ga ik altijd een stapje verder dan dat ik zelf zou doen. Heerlijk!
Jij moest en zou gewoon als paranimf naast me staan. Dat was voor mij geen twijfel. Heel bijzonder dat jij ook naast me wilde staan. Bedankt hiervoor.

Drs. J. Groenewoud, beste Hans, mijn SPSS-goeroe. Mijn eerste kennismaking met jou was tijdens de lessen SPSS voor het blok ‘onderzoek’ tijdens de Masteropleiding. Wie had toen gedacht dat we samen zo vaak zouden zitten bomen over de statistische analyses van dit hele project. Iedere keer opnieuw legde je me vol geduld de statistiek uit. Dank voor alles wat je me hebt geleerd. Ik weet je nog steeds te vinden, hoor!

Ik ben ook veel dank verschuldigd aan Lauren Bullens en Ninke Schrijvers. Toenmalig medisch studenten en inmiddels alweer veel verder in hun carrière. Dank voor jullie zeer belangrijke bijdrage aan deze onderzoeken.

Mevr. Mallens, Wies Walter, Sue Farmer, Johanna Hopper-Kroekenstoel en Sonny van der Sanden. Dank allen voor de taalkundige correcties!

De manuscriptcommissie.
Bij dezen wil ik de leden van de manuscriptcommissie, Prof. dr. T. Achterberg, Prof. dr. H. Lafeber en Prof dr M. Hulscher, hartelijk danken voor het beoordelen van het manuscript in jullie toch al zo druk bezette tijd.

Infuuswerkgroep neonatologie.
Bijzondere dank aan alle verpleegkundigen met wie ik met veel plezier heb samengewerkt in de infuuswerkgroep. Wat hebben we samen veel werk verzet! En wat hebben jullie veel bijgedragen aan al deze onderzoeken. Kritische noot, data mee verzamelen, training on the job. Zonder jullie had ik dit nooit gered.
Er zijn echter twee personen die ik speciaal wil bedanken, zonder daarbij alle andere collega’s tekort te doen.
Speciale dank aan Mieke Verhoeven. Jij bent degene die me bij de infuuswerkgroep hebt geïntroduceerd. Wat heb ik van jou veel geleerd in het infuusvak. No nonsens, hoofdrekenen (wat is een rekenmachientje?). In één woord ‘practical nurse’ pur sang! Inmiddels geniet je alweer enkele jaren van je welverdiende pensioen.
Speciale dank ook aan Gea. Nog zo’n klinische, praktische verpleegkundige. Wars van pamperen en protocollen. Regelmatig hoor ik je nog zeggen: “Wat protocollen! Hoe zit het met het gezonde verstand van ons, verpleegkundigen!” En hoe gelijk heb je. Maar toch begreep je ook de noodzaak van het papierwerk en protocollen. Dank voor je kritische noot en steun!

Theo Peeters en Petri Mansvelt, dank voor jullie steun, het delen van de taken in de toen nieuwe functie van ons als verpleegkundig specialisten op de NICU en het aanmoedigen van het verrichten van dit onderzoek.

Verpleegkundigen neonatologie.
Voordat ik iedereen bedank, wil ik 3 verpleegkundigen die tijdens deze studies zijn overleden, apart benoemen
Als eerste: Henriette Wilbers. Henriette was vooral actief binnen de ECMO werkgroep. Maar voor mij was zij de eerste verpleegkundige die mijn ogen opende voor het belang van verpleegkundig onderzoek. Ik weet heel zeker dat, wanneer het voor Henriette anders was gelopen, zij mij voor zou zijn gegaan in verpleegkundig onderzoek en het maken en verdedigen van een proefschrift.
Als tweede: Marie-Jose Geist. Samen hebben we de kinderaantekening gedaan en kwamen we elkaar weer op neonatologie tegen. Wat een gedreven collega. Bij elk onderzoek werkte ze vol overgave mee, maar stelde ze ook kritische vragen waardoor ik weer een verbeterslag kon maken. Neonatologie mist je als gedreven en hartelijke collega.
Als derde: Ans Heijnen. Als ik aan Ans denk word ik stil.
Zo puur, integer, oprecht. Als collega, lid van de infuuswerkgroep en later als senior met als aandachtsgebied “onderzoek” hebben we samen zoveel gedeeld wat betreft deze onderzoeken. Als ik er niet was nam Ans het over, hoe ziek ze ook was. Lieve Ans, ik denk nog vaak aan je. Jij had hier naast mij moeten staan.
Dan alle andere collega’s van de neonatale intensive care, high care en medium care. Mijn dank voor alle heerlijke jaren werkplezier, ondersteuning bij al mijn ‘projectjes’, het invullen van weer een vragenlijst of het bijhouden van nog een afkruislijst. Hoe trots ben ik dat een deel hiervan inmiddels gedigitaliseerd is en verdere voortgang heeft.
Koester de bijzondere sfeer op de afdeling. Als je er middenin zit, merk je dit misschien wat minder. Maar nu, op afstand, kan ik alleen maar zeggen hoe bijzonder deze sfeer is.

Neonatologen, fellows, arts-assistenten, secretariaat, voedingsassistenten van neonatologie, dank voor jullie steun en zeer fijne samenwerking.

Afdeling Pijn en Palliatieve zorg.
Verpleegkundigen, artsen, fysiotherapeuten, psychologen, secretariaat en OK team neuromodulatie. Dank voor het feit dat jullie me zo in jullie team hebben opgenomen. Ik voel me hier thuis en hoop nog veel mooie momenten met jullie te beleven. Speciale dank aan Prof. dr. K. Visser, voor iedere keer weer de bemoedigende woorden en het vertrouwen dat je me gaf om door te gaan met de promotie. Marijke Dijkstra, verpleegkundig manager, dank voor de ondersteuning.
Apart wil ik nog Paul Verstegen noemen. Jij bent degene die me aan de hand hebt genomen in het ‘land der neuromodulatie’. Wat heb ik veel van je geleerd. Dank voor je blijvende enthousiaste ondersteuning, ook voor dit proefschrift. Speciale dank voor jouw artistieke steun bij het maken van de voorkant van het boekje. Dat je dit hebt willen doen, ondanks dat je een hele andere besteding van je tijd had kunnen hebben, vind ik heel bijzonder.

Lieve vrienden.
Eindelijk is het zover! Zal ik nu echt meer tijd krijgen om weer een potje te tennissen, een bakje koffie te drinken, een borrel te pakken of even een lekkere wandeling te maken? Ik hoop het uit de grond van mijn hart. Want ik heb dit gemist!!
Dank voor jullie begrip en ondersteuning.

Lieve schoonouders, Masja en Paul, Harm en Esther en stoere neven en nichtje.
Bedankt voor jullie belangstelling en ondersteuning, de heerlijke maaltijden, gewoon alles. Jullie zijn heel belangrijk voor mij. Ik hoop nog heel veel jaren met jullie te mogen doorbrengen.

Lieve pap, mam, Mariëlle en Eugène, Barton en Angeline en mooie nichten en stoere neef.
Het was soms heel moeilijk uit te leggen wat een impact dit proefschrift had op deze laatste jaren. Maar jullie bleven me steunen, ondanks dat dit invloed had op andere momenten waar verdeling van aandacht en zorg en ook jullie tijd erg belangrijk was. Hoe kan ik jullie danken voor dit begrip. Maar nu is het zover en hoop ik met heel mijn hart meer ruimte te krijgen om er ook voor jullie te zijn. Hoe trots ben ik om deze mijlpaal samen met jullie te mogen beleven.

En dan lieve Gerben.
Als ik terugdenk aan de laatste jaren word ik een beetje stil. Jij zegt wel dat jij niets voor mij hebt gedaan, maar het tegendeel is waar. Hoe vaak zat ik bij je…maar ook weer niet. Vroeg je me iets….en knikte ik afwezig. Op momenten waar ik het echt even niet meer zag zitten stond jij daar met je nuchtere kijk op het leven, met je onuitputtelijke relativeringsvermogen, met je humor en met je warmte. Zonder jou was ik niet zover gekomen. Dat weet ik zeker! Ik hoop nog heel veel mooie jaren met je te hebben en heel veel reizen samen te mogen beleven. Dank voor alles.

Curriculum Vitae

Inge Arnts was born in Ooy- Persingen on 20 November 1968 as the third child in her family. She spent her childhood in this small village. After finishing High School (1981-1986) she studied at the Nurse Academy (Hogere Beroeps opleiding Verpleegkundige, HBOV 1986-1990) in Nijmegen although she would have preferred the In-Service School because of the practical skills. However, her experiences studying nursing at the HBOV were instrumental in her career choices. Inge would have liked to specialize in pediatric nursing but was offered an internship in chronic healthcare during her training as a nurse. Shortly before she started, she was offered an internship in pediatric neurology. An opportunity she took with both hands, and one she has not regretted since.

Subsequent to her training and upon her graduation she was offered a position as a registered nurse at the pediatric neurology department. There, Inge continued her training in the field (nurse manager: G. van Neerven). In this department she graduated for the training pediatric nursing care (1991-1992) and for children with neurological impairment and diseases (1993). This is also were she gained her first experience in presenting at national symposia.

After four years in the pediatric neurology department, she started working in the Neonatal Intensive Care Unit (NICU), where she followed additional training and graduated as neonatal intensive care nurse (1994-1995, nurse manager: T. Vanlier, later H. Hendriks).

Over the years, she developed an interest in the management of pain and the use of intravenous devices. Working in the infusion nursing team and the pain nursing team, Inge and her team developed and implemented protocols and innovations. In the beginning she was involved in the teaching of pain and infusion care at the NICU nursing course. This course was later extended to include the teaching of physical examinations of newborns for phycisican assistants, and circulation and research for regular nurses.

She graduated for her Master's degree in Advanced Nursing Practice (Hogeschool Arnhem Nijmegen in 2003-2005). Simultaneously, she followed two extra theoretical and clinical teaching courses during six months at the Hanze High School, Eindhoven in 2004. During these studies, Inge became aware of the importance of research. Dr K.D. Liem stimulated her interest in research and challenged her to translate clinical questions into research questions and was very supportive of her development in research. As a result, Inge presented the results of her studies on national and international symposia. A highlight in Inge's career was when her team received the Patient Safety Care Award for Radboud UMC departments for their research in diminishing CLABSI (2012). This research project was also shortlisted for the National Safety Award in 2012. Again, thanks to Dr Liem who was the driving force behind all these endeavours.

In collaboration with her colleague Ronald van Rens (Erasmus Medical Center, Rotterdam) she founded the National Infusion Group together with other colleagues. Their main objective was sharing information in order to develop the best infusion therapy for neonates.

In 2011, after 17 years working as nurse and Nurse Practitioner at the NICU, she took the next step in her career and started as Nurse Practitioner with the Pain and Palliative Care department, with a special focus on neuromodulation.
A new challenge and new opportunities!
Inge Arnts is happily married to Gerben Brugman. They have been living in Grave since 1992.

STELLINGEN

behorende bij het proefschrift

Managing the complications of intravenous devices in the neonatal intensive care unit:

A contribution to patient safety

Inge Arnts

1. Het gebruik van heparine voor het open houden van intraveneuze slotjes is bij neonaten niet zinvol, doch eerder potentieel gevaarlijk en dus ongewenst in het kader van patiëntveiligheid. *(dit proefschrift)*
2. Het in de literatuur hanteren van verschillende definities van CLABSI (central line associated blood stream infection) bij neonaten maakt het vergelijken van de uitkomsten moeilijk. *(dit proefschrift)*
3. Het hebben van een navelcatheter is geen contra-indicatie voor het verzorgen van een pasgeborene in buikligging. *(dit proefschrift)*
4. Het invoeren van een preventieve CLABSI bundel is een eenvoudige en kosten effectieve maatregel ter preventie van CLABSI bij neonaten welke bijdraagt aan de patiëntveiligheid. *(Dit proefschrift)*
5. Een belangrijk onderdeel van de preventieve bundel ter voorkoming van CLABSI is het dagelijks kritisch beoordelen of de lijn verwijderd kan worden. (dit proefschrift)
6. Een speciaal 'infusion team' draagt bij aan reductie van CLABSI. *(Legemaat MM et al, Int J Nurs Stud. 2015;52(5):1003-1010)*
7. Transparantie van de uitkomsten van behandelingen of onderzoeken binnen het eigen team, vergroot de persoonlijke betrokkenheid en verantwoordelijkheid, wat een gunstig effect heeft op de uitkomsten. *(Suresh GK et al, Am J Perinatol. 2012; 29(1):57–64)*
8. Pijn is wat een patiënt zegt dat het is en treedt op wanneer de patiënt zegt dat het optreedt. *(Mc Caffery)*
9. Dit jaar is de Nederlandse gezondheidszorg opnieuw als beste van Europa beoordeeld wat toegeschreven zou kunnen worden aan het systeem van de private markt van de zorgverzekeraars, de huisarts als poortwachter en de hoge graad van de betrokkenheid van patiëntorganisaties in beleidsvorming rondom de gezondheidszorg. *(Euro Health Consumer Index,Health Consumer Powerhouse, Sweden, 27-01-2015)*
10. Hoe goed je alles ook voorbereidt, je doet het pas echt goed als je rekening houdt met onverwachte elementen en je je daaraan kan aanpassen. (Mijn vader)
11. Vriendschap vergroot het geluk en vermindert ellende door onze vreugden te verdubbelen en ons verdriet te delen. *(Joseph Addison)*
12. Logica brengt je van A naar B, maar fantasie brengt je overal. *(Albert Einstein)*

Uitnodiging

voor het bijwonen van
de openbare verdediging
van het proefschrift

Managing the complications of intravenous devices in the neonatal intensive care unit:
A contribution to patient safety

op woensdag 23 september 2015
om 16.30 precies in de aula van
de Radboud Universiteit Nijmegen
Comeniuslaan 2 te Nijmegen.

U bent van harte welkom bij
deze plechtigheid en de aansluitende
receptie ter plaatse tot 18:45 uur.

Inge Arnts
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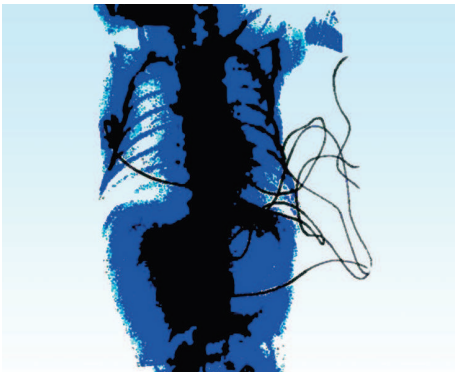

Paranimfen

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