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ORIGINAL ARTICLE

Risk factors associated with complications of peripherally inserted central catheter in newborn infants

Factores de riesgo asociados a complicaciones de catéteres centrales de inserción periférica en recién nacidos

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What do we know about the subject matter of this study?

Peripherally inserted central venous catheters allow reliable access and longer duration in neonates, but sometimes present major complications such as infection and thrombosis which are associated with lower gestational age and prolonged use.

What does this study contribute to what is already known?

Major complications occurred in 4% of patients, including infections and effusions due to extravasation. Their association with GA and use 14 days were confirmed. Infections were associated with number of punctures, and the non-infectious ones with the use of the upper extremities and malposition.

Abstract

Objective: To describe the outcome and associated complications with the use of peripherally inserted central venous catheters in neonates, and to identify risk factors associated with the presence of major complications. **Subjects and Method:** Analytical study of the follow-up of catheters placed in 541 neonates hospitalized in a neonatal intensive care unit. Outcome and complications were described. To assess risk factors associated with major complications, multivariate logistic regression analysis was used. **Results:** 655 catheters were placed in 541 infants with birth-weight ranging from 420g to 4.575g. The mean duration was 11.6 ± 8.5 days. 29 patients (4.4%) presented major complications, and associated bloodstream infection was the most frequent (n = 17), determining an infection rate of 2.25 ‰ catheter days. Infections were more frequent among catheters lasting > 14 days: 9/179 (5%) vs 8/476 (1.7%) of those lasting ≤ 14 days ($p < 0.05$). Other complications included: pleural effusion due to extravasation (n = 6) and atrial thrombosis (n = 3). Multivariate analysis showed that

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the presence of major complications was associated with a gestational age < 28 weeks: OR 5.9 (95% CI 1.2 to 40), and upper extremities use: OR 3.2 (95% CI 1.1-7.0). Infections were associated with a greater number of punctures during placement: OR 2.1 (95% CI 1.2-4.8) for each puncture and gestational age < 28 weeks: OR 7.9 (95% CI: 1.4-73). **Conclusion:** The use of catheters was long-lasting and with a low rate of major complications, which were more common in extremely preterm infants. Infections were associated with an increased number of punctures and duration > 14 days. Other complications were more frequent when upper extremities insertion was used.

Introduction

In recent years, due to advances in neonatal intensive care, very low birth weight (VLBW) newborns and those with severe pathologies and/or complex malformations have had a significant improvement in survival[1-3]. Their hospital stay may be prolonged, requiring complex therapies and venous access for a longer period. Therefore, different techniques have been proposed to have better quality and permanent venous accesses[4,5].

For decades, central catheters have been used in neonatology, however, their prolonged use has been associated with infections and other complications[6-8]. Among the alternative techniques is the percutaneous insertion of silicone catheters through a peripheral vein, known as peripherally inserted central catheters (PICC) or percutaneous catheters. This is used in newborns who require intravenous treatments for periods longer than 7 days. National and international experiences demonstrate several advantages such as less insertion trauma, longer duration, and reliability of the accesses[9-13].

The insertion is relatively easy and can be performed in the patient's unit. However, both major (life-threatening) and minor complications have been described with its use. Major complications are bloodstream infections (BSI), arrhythmias, and pericardial and pleural effusions[14-18], and minor complications include phlebitis, fluid infiltration/extravasation, and obstruction[10,12,18].

The objective of this study is to describe the evolution and complications of the use of PICC in a tertiary neonatal intensive care unit and to identify the risk factors associated with the occurrence of major complications.

Subjects and Method

Analytical and retrospective study based on prospectively collected data for the follow-up of PICC lines inserted in the Neonatology Service of the Clinical Hospital of the UC-CHRISTUS Health Network, between January 1998 and December 2014. Hospitalized newbors that required the insertion of a PICC line were included. Those with a PICC inserted in another service and those who were transferred to other centers with a PICC *in situ* were excluded from the analysis.

The catheters used were 1 or 2 French size/gauge (24 to 28) silicone catheters, radiopaque, with a single straight terminal orifice, 30 to 40 cm long. Insertion was performed in the patient's unit and the location of the catheter tip was controlled radiologically. It was indicated that when the catheter was inserted from an upper extremity, the tip should be in the superior vena cava (SVC) or at the junction of the SVC and the right atrium, and when inserted from a lower extremity, the tip of the catheter should be above the L4-L5 vertebrae, but not in the heart. After an imaging control, it was attached with sterile adhesive tape (Steri-strip®) 1 cm from the insertion site. The remaining part of the catheter outside the insertion site was attached rolled around to the skin with the same tape and covered with transparent film dressing (Tegaderm®). The insertion site was covered with a sterile 1x1 cm gauze dressing and attached with sterile adhesive tape. Follow-up included daily observation and removal according to the standardized protocol of the service[9]. Cleansing and dressing were performed every 48 hours using chlorhexidine 0.5% in alcohol and gauze dressing. The PICC lines were maintained with a base infusion, either parenteral nutrition or glucose solution with electrolytes with the addition of heparin (0.5-1UI/ml).

A standardized data collection sheet was used, which was completed prospectively during the patient's hospitalization. The variables included in the registry were birth weight, sex, gestational age (GA), Apgar score, admission diagnoses, age at insertion, number of punctures, insertion site, tip location, days of stay, and cause of catheter removal. "Long duration" was defined as those who had the catheter for longer than 7 days. We also recorded possible major complications such as sepsis, pleural or pericardial effusion, inadvertent catheterization of unusual vessels, and atrial or major vessels thrombosis; and minor complications such as phlebitis, infiltration/extravasation, obstruction, displacement or involuntary removal, and catheter section. Catheter-as-

sociated BSI was defined as the presence of at least one peripheral blood culture (+) associated with clinical deterioration while the patient had the catheter *in situ* and no evidence of infection elsewhere.

Statistical analysis

The JMP 9 Software (SAS Institute, NC, USA) was used for data analysis. Measures of central tendency and dispersion were used to describe the results. For comparisons of continuous variables, Student's t-tests or Mann-Whitney tests were used. Categorical variables were compared with the Chi-square test and, if the number of observations was < 5, Fisher's exact test was used. A p-value < 0.05 was considered significant. To identify and weight risk factors associated with major complications, multivariate logistic regression analysis was performed. Two models were performed, one to evaluate factors associated with non-infectious complications and the second one to analyze factors associated with the incidence of catheter-related infection.

This study was approved by the Scientific Ethical Committee of Health Sciences of the Catholic University of Chile with waiver of informed consent since the data are from a standard procedure in neonatal intensive care, which were collected from the internal records of the Service and transferred to an anonymous database without the identification of the patients involved.

Results

655 catheters inserted in 541 NBs were studied, the mean duration was 11.6 ± 8.5 days, ranging from 1 to 64 days, 429 (65%) of them stayed for more than 7 days. This results in 7,539 catheters days. The mean GA of the infants was 31.3 ± 4.7 weeks, ranging from 23 to 41 weeks. Their mean birth weight was 1698 ± 984 g, with a range between 420 g and 4575 g. Among the most frequent diagnoses of the NBs who required PICC were 302 (56%) cases of VLBW, 78 (14%) persistent pulmonary hypertension, 48 (9%) diaphragmatic hernia, 32 (6%) congenital heart disease, and 28 (5%) cases of other gastrointestinal malformations.

Of the total catheters inserted, 44.9% were inserted on the first attempt, with a mean of 2.2 ± 1.4 punctures, and a range of 1 to 7 punctures. The most frequent insertion site was the upper extremities in 80.1% (elbow crease, hand, forearm, and axilla), and 56% of them were on the right side. 15.9% were inserted in the lower extremities and 4.0% in neck veins. The most frequent reason for removal was the end of treatment (60.2%). Major complications occurred in 29 catheters (4.4%), the most frequent was BSI in 17 (2.6%), which determined an infection rate of 2.25 per 1000 catheter/days (Table 1).

The microorganisms isolated in catheter-associated BSI were *coagulase-negative Staphylococci*[7], *Candida albicans*[6], *Pseudomona aeruginosa*[1], *Klebsiella oxytoca*[1], *Staphylococcus aureus*[1], and *Enterococcus faecalis*[1]. One patient presented co-infection by two agents (*Staphylococcus epidermidis* and *Candida*). Catheter-associated infection occurred more frequently in extremely low birth weight preterm infants (< 1000 g), with a rate of 4.98 per 1000 catheter/days (Table 2).

The longer the catheter duration, the higher the infection risk, especially in those catheters that remained > 14 days, where 9/179 (5%) presented BSI, which was significantly higher than those who remained < 14 days (p < 0.05), where only 8/476 (1.7%) were affected (Table 3). However, several catheters remained > 21 days without infection, and even the rate dropped after the third week.

In the multivariate analysis, the presence of catheter-associated BSI was associated with a GA under 28 weeks and a higher number of punctures during its insertion (Table 4). There was also a trend of increasing risk with catheter duration (OR 1.9, CI 95% 0.9-5.1) for each additional week (p = 0.1).

Among the major non-infectious complications observed were the development of liquid collections due to extravasation in the pleural (n = 6) or pericardial space (n = 1), and the presence of right atrial thrombus (n = 3). One of the extreme preterm infants died due to progressive respiratory deterioration after extravasation with massive pleural effusion. The other 6 cases of extravasation effusions could be managed with catheter removal, drainage of the collection, and transient increase of their respiratory therapy.

In 6 of the 7 patients who presented with effusions, there was evidence of mal positioning of the catheter tip, either at the time of insertion or because it had been displaced subsequently. In 5 of them, the catheter tip was in the subclavian vein without reaching the SVC. The multivariate analysis showed that these major non-infectious complications were significantly associated with a GA < 28 weeks and with their insertion in the upper extremities, which had a 3 times higher risk of developing these complications than those inserted in the lower extremities (Table 5).

27.4% of all catheters presented minor complications (Table 1), with phlebitis in 10.5% and obstruction in 7.0% as the most frequent.

Discussion

In our Neonatology Department, PICC lines have been inserted since the '90s, and it is a common procedure in neonatal intensive care. In this study, we highlight that the use of PICC lines was of long dura-

Table 1. Complications associated to PICC observed in this group.

	Complication	n	%
Mayor Complications (29 = 4.4%)	BSI/CVC	17	2.6 %
	Pleural effusion	6	1.2 %
	Pericardial effusion	1	0.15%
	Atrial Thrombosis	3	0.5%
	Displacement to spine or retroperitoneal	2	0.3 %
Minor Complications (182 = 27.8%)	Phlebitis	69	10.5 %
	Obstruction	46	7.0%
	Infiltration/extravasation and limb edema	44	6.7%
	Displacement or inadvertent withdrawal	17	2.6%
	Catheter section/rupture	6	0.9 %

BSI: Blood Stream Infection; CVC: Central venous catheter

Table 2. Relationship between birth weight and PICC infection

Weight cathegory	< 1000 g	1001-1500 g	> 1500 g	Total
Catheters (n)	201	175	279	655
Catheter days (n)	2009	1676	3747	7539
BSI: n (%)	10 (5.0%)	3 (1.7%)	4 (1.4%)	17 (2.6%)
Rate /1000 cath days	4.98	1.79	1.07	2.25

Minsal Infection Rate in pediatric patients: 3.41‰ catheter days (2012). BSI: Blood stream infection

Table 3. Relationship between infection and catheter duration (per week)

Catheter duration (days)	0-7	8-14	15-21	> 21	Total
Catheters (n)	655	429	179	67	655
Catheter days	3899	5381	3413	2010	7539
BSI (n)	3	5	7	2	17
Infection rate %	0.5%	1.1%	3.9%	3.0%	2.6%
Infection rate/1000 days	0.7	0.93	2.1	1.0	2.25

BSI: Bloodstream Infection

tion and with a low rate of major complications. The presence of these complications was significantly associated with a GA < 28 weeks, the development of BSI was related to a greater number of punctures during insertion and duration longer than 2 weeks, and insertion in the lower extremities was associated with a lower risk of non-infectious complications.

The most frequently observed major complication in the sample was BSI, with a rate of 2.25 per 1000 catheters/day. Although this rate is lower than that observed by the Chilean Ministry of Health for pediatric patients in 2012 (3.41 per 1000 catheter/days)[19], there are no specific national standards for PICC in NBs, nor are they divided by GA or birth weight cathegories, there are only standards for umbilical catheters. The rate reported in this study is similar to recent international reports[15,20-24].

In this study, we identified that the risk factors associated with a higher incidence of BSI were a GA < 28 weeks and a higher number of punctures during catheter insertion. Many authors have described the association between infection and lower GA, especially in preterm infants < 1000 g, due to the deficiency in their immune system and the requirements of prolonged invasive therapies[21-23].

Regarding the number of punctures during insertion, we found that for each additional puncture, the risk of infection increased by 2.1 times. This is an

Table 4. Risk factos for catheter associated infections. Odds Ratios and their 95% confidence intervals.

Factor	*Odds Ratio*	95% confidence interval	p-value
Birth weight (per 100 g ↓)	1.3	0.3 - 3.7	0.3
Gestational age < 28 weeks	7.9	1.4 – 73	< 0.03
Masculine gender	2.1	0.6 – 8.7	0.25
5 min Apgar ≤ 5	1.8	0.2 – 8.8	0.51
N° punctions (x punction)	2.1	1.3 – 4.8	< 0.01
Upper extremities location	2.2	0.4 – 9.1	0.3
Catheter duration (per week ↑)	1.9	0.9 – 5.1	0.1

Table 5. Risk factors for catheter associated major complications. Odds Ratios and their 95% confidence intervals.

Factor	*Odds Ratio*	95% confidence interval	p-value
Birth weight (per 100 g ↓)	1.4	0.4 - 4.7	0.26
Gestational age < 28 weeks	5.9	1.2 – 40	< 0.04
Masculine Gender	1.4	0.4 – 4.2	0.5
5 min Apgar ≤ 5	1.2	0.2 – 5.2	0.8
Upper Extremities location	3.2	1.1 – 9.7	< 0.05
Catheter duration (per week ↑)	1.7	0.5 – 7.3	0.4

important observation that has been evaluated in few studies. Njere et al. found no association between the frequency of infection and the number of insertion attempts, but in that report, there were few children with a very high rate of infection[25]. In this study, the number of punctures was thoroughly recorded which showed an evident increase in the risk of BSI with the higher number of attempts. It is therefore very important to take extreme hygiene measures during insertion, and if a first attempt was unsuccessful, to use new equipment and sterile dressing, and to sanitize the area well before performing a new puncture.

Similar to other reports, a greater number of days of catheter permanence was related to a higher rate of infection, especially if they remained more than 14 days[20-22]. However, we had a significant number of catheters that lasted more than 21 days without infection, and even the rate dropped slightly after the third week, therefore, in the multivariate analysis, the increased risk per week of duration had less impact. This is similar to that reported by Milstone et al, in one of the largest series of follow-up of PICC and its relationship with infection in NBs[21]. They describe a significant increase in the risk of BSI with catheter duration for the first 14 days, after which the infection rate, although remaining high, increased at a lower rate. Among the factors that could explain this difference with other reports is the lesser intervention and the cleansing and dressing performed in our service.

The most frequent microorganism was *coagulase-negative Staphylococcus*, which is in line with other reports[21-23]. The second most frequent microorganism was *Candida albicans*, which was observed mainly in extremely preterm infants and some NBs with malformations that required complex surgical procedures. Interestingly, fungal sepsis decreased and almost disappeared in the second period (from 2009 onwards), which was associated with the restricted use of broad-spectrum antibiotics in the service[26].

Major non-infectious complications included the development of liquid collections due to extravasation in the pleural or pericardial space and atrial thrombosis. These were related to an inadequate location of the catheter tip, which has also been described in other publications[16-20]. Therefore, it is essential to perform an adequate measurement of the length to be introduced and to monitor radiologically the location of the tip after its insertion with two projections (anteroposterior and lateral). It is also very important to re-evaluate whenever the catheter is moved for its relocation or has been displaced from its original attachment site.

The position in the subclavian vein should not be considered appropriate, as we saw in this series 5 of the 7 cases of effusion were associated with this position. It is also very important to have radiopaque catheters that allow better visualization. The use of ultrasound is a useful tool both for the insertion of central catheters and for verifying their location[27]. It is also necessary to

consider that catheters can move or migrate, so it is important to re-evaluate their position in successive controls. We suggest at least every 7 days if the catheter remains for long periods.

In this series, we also observed displacements towards the retroperitoneal space, and in one patient towards the epidural space. These corresponded to catheters inserted in the lower extremities, and although this is infrequent, it has been previously described[28,29]. Two radiographic projections (anteroposterior and lateral) help to confirm the position. In lower extremities, the catheters' tip may inadvertently be in an ascending lumbar vein and may appear to be in a good position on the anteroposterior view[28].

Interestingly, in this study, we observed a lower frequency of serious non-infectious complications in those catheters inserted in the lower extremities. Several studies have shown a higher incidence of complications with upper extremity PICC, which has been related to a higher frequency of tip malposition[17,18,30,31].

Among the minor complications, phlebitis stood out, which occurred in 10.5% of the cases, similar to what has been reported in other series[15,20]. This was observed more frequently in smaller patients, in most cases, it was transitory and was not associated with infection. The size of the vein in relation to the diameter of the catheter is one of the factors that could influence its appearance. Chemical phlebitis has also been described in relation to the talcum powder in gloves used in the insertion, recommending the use of talc-free gloves[13].

The type of catheter material and the movement of the catheter inside the vessel can irritate, so adequate immobilization and the use of silicone catheters would help to reduce phlebitis[9,20]. Catheter occlusion occurred in 6.9%, a lower rate than that published in other studies[14,20]. In our practice, it is usual to add heparin to the infused solutions (0.5-1 IU x ml)[32,33]. We do not collect blood samples for testing or administer blood transfusions through them, which is recommended for catheters ≤ 2 French[13].

Among the strengths of this study are the large sample size and the variety of NBs included, which allows showing the incidence of complications and to better identify the associated risk factors. Among its weaknesses are not having the follow-up of the NBs who were transferred with PICC to other centers and not having the registry of failed insertions. On the other hand, during the long period of the study (15 years), there were changes in some practices that could affect the results, such as the use of antibiotics in the unit. The implementation of care bundles to reduce infections in the service, which in recent years restricted the use of broad-spectrum antibiotics, may have influenced the lower incidence of BSIs observed[26]. Among these measures, we also highlight the insistence on a thorough hand washing with chlorhexidine soap and subsequent paint with chlorhexidine in alcohol before insertion.

In conclusion, the use of PICC in this group of NBs resulted in a long duration of PICC and a low rate of major complications which mostly occurred in extremely preterm infants. BSIs were associated with a greater number of punctures attempts and a duration of more than 14 days. The other complications were more frequently associated with insertion in the upper extremities and tip malposition. Explicit care protocols, with strict follow-up and control, incorporating new evidence and systematic training of personnel, are essential for the successful use of these catheters and to avoid possible complications.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors state that the information has been obtained anonymously from previous data, therefore, Research Ethics Committee, in its discretion, has exempted from obtaining an informed consent, which is recorded in the respective form.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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