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Original article

Heparin in peripherally inserted central catheters did not alter elective removal and complication rates in preterm infants

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SUMMARY

Background & aims: In preterm and sick newborn infants, peripherally inserted central catheters (PICC) are used for the delivery of concentrated parenteral nutrition and other high risk drugs. Despite the precaution issued by the ESPGHAN 2018, heparin is used in many neonatal intensive care units (NICU) and is thought to extend PICC usability. This study aimed to examine the association of prophylactic heparin with elective PICC removal rates, with complication rates and dwell-times.

Methods: All PICCs placed at two different Level III NICUs during 2017, were analyzed retrospectively. Out of 168 PICCs, 36 had to be excluded, leaving 132 PICCs for analysis. Prophylactic heparin was used in 90 PICCs (heparin-group) and 42 PICCs without (control group)

Results: Sixty-six PICCs (73 %) vs 30 (71 %) could be removed electively in the heparin-group (adjusted Odds Ratio 95 % confidence interval (CI) 0.95 [0.31, 2.89], $p > 0.9$). Complications occurred in 17 (19 %) and 8 (19 %) PICCs in the heparin-group and control-group, respectively. Dwell-times did not differ significantly with median 10 days (Interquartile range (IQR) 6,17) in the heparin-group and 8 days (IQR 7,12) in the control-group with an adjusted hazard ratio 0.70 (95 % CI [0.45, 1.09], $p = 0.11$).

Conclusion: In our retrospective analysis, adding heparin to admixtures infused via PICCs did not alter the odds of elective removals or complication rates. Furthermore, Dwell-times did not differ significantly between the two groups. In line with the ESPGHAN recommendations, our data can not support the use of heparin to improve PICC usability.

1. Introduction

Central catheters are a precondition for the delivery of concentrated nutrition solutions and critical medications to sick patients. In infants, apart from umbilical catheters, peripherally inserted central lines (PICC) are predominantly used on neonatal intensive units (NICU) worldwide. Optimally, the PICCs should be maintained useable during the whole treatment period.

To maintain this goal and extend the usability of PICCs the anticoagulant drug heparin is frequently used on many NICUs, but until today only a limited number of studies have verified a positive effect on PICC survival. Though, the mechanism of function of heparin seem rational, the optimal dosing regime is yet unknown and heparin dosing varies widely between centers [1].

In 2018 the ESPGHAN concluded that the prophylactic use of heparin has the potential to increase the patency of PICCs, but at the same time they discouraged the use due to potential harmful side effects in newborn and preterm born infants. These side effects include intracranial hemorrhages, thrombocytopenia and destabilization of lipid emulsion causing lipid emboli [2]. The statement regarding the side effects was based on nine studies and one Cochrane meta analysis (including 477 infants from three studies with different heparin dose and application methods) published at that point.

Abbreviations: PICC, Peripherally inserted central catheter; HG, Heparin group; CG, Non heparin (control) group; CLABSI, Central line-associated bloodstream infection.

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Additionally, the ESPGHAN statement regarding the increased PICC patency was based on one randomized controlled trial (RCT) in which no effect of heparin on catheter patency could be found and the Cochrane meta analysis by Shah and Shah [3,4]. The Cochrane meta analysis included three trials with different dose and application regimes and concluded that adding heparin to the PICC could extend their patency, but caution should be warranted regarding heparin side effects [4–6].

In contrast to the Cochrane analysis, Bin-Nun et al. included two more RCTs and one retrospective study in a review published in 2016 with an in depth analysis of heparin doses used. They concluded that clinicians need a practical therapeutic approach while awaiting supplementary data, with the recommendation that a heparin dose of 10–50 IU/kg/day, could increase the usability of long lines [7].

In one of the more recent studies, Uslu et al. described a 2.7 days increased PICC durability in the heparin group. In contrast, Isemann et al. could not find any difference when comparing two periods with and without additional heparin in PICCs [8,9].

Taking this small and conflicting body of evidence and the possibility of harmful side effects into account, it would be desirable to gain clear evidence if prophylactic heparin improves PICC patency. As heparin is classified as high alert medication by the Institute for Safe Medication Practices (https://www.ismp.org) and the European association of hospital pharmacists (https://www.eahp.eu) it would be preferable if the prophylactic use of heparin could be safely omitted.

The aim of this retrospective study was to investigate the effect of heparin on elective (planned) PICC removal rates, catheter associated complication rates and PICC durability in preterm infants at two high level NICUs at the Karolinska University Hospital.

2. Methods

This study was a non-interventional, retrospective chart review, analyzing all PICCs inserted in infants treated at two different Level III NICUs at the Karolinska University Hospital in Stockholm between January 1st and December 31st, 2017. A detailed description of catheter placement success rates, final tip position and insertion site associated complications rates are published elsewhere [10].

Eligible for inclusion were all PICCs deemed useable during this time period. If infants received multiple PICCs during the period, all catheters were included in the study. Infants transferred to a facility outside the Karolinska University Hospital with a PICC in situ ($n = 32$) were excluded from analysis due to missing data regarding PICC-elimination. Incomplete chart records ($n = 2$) or undocumented reasons for PICC-removal ($n = 2$) were excluded (Fig. 1).

2.1. Definitions

Elective removal, as the primary outcome, was defined as planned elimination at the end of the treatment period. Removal due to any kind of catheter related problem or complication, earlier than intended, was classified as non-elective removal.

PICCs were categorized into the heparin group when at least one solution containing heparin was infused through the PICC for at least one day.

Dwell-times were calculated including the first and the last day of catheter usage.

Central line associated infection was defined as a positive blood culture, taken when signs of infection were present while the central line was in situ. Infections are further referred to as central-line associated bloodstream infection (CLABSI).

2.2. PICC placement and tip position verification

Single lumen 15 or 30 cm 24G PICCs (Vygon, Skellefteå, Sweden) were inserted by an experienced nurse or medical doctor at the site of their choice after direct vein visualization and palpation. Ultrasound was not used except for one case where the malpositioning of the PICC in the aorta was confirmed before removal. In case the line was too long, it was never trimmed, but instead left coiled on the outside under an occlusive dressing. The position was determined by anteroposterior, and in most cases additional lateral, chest radiography with the arms and legs in supine anatomical position. Detailed information about x-ray interpretation and final PICC tip classification have been published before and can be obtained from Supplemental Table S1 [10].

2.3. Data acquisition

Data was extracted from the patient's electronic journal for baseline demographics, the PICC insertion and removal, infant's weight and date of insertion, reason for removal (elective, non-elective) and category of non-elective removal (PICC-related malfunction, vessel related harm, infection, malpositioning or post-mortem removal) and were stored anonymized in an Excel sheet. The contents of the solutions infused via the PICC were exported for every day of catheter usage. Heparin was typically infused as addition to the individual parenteral nutrition admixture in a dose of 20 IU/100 ml parenteral nutrition admixture.

2.4. Statistical analysis

Median, interquartile range (IQR) and number (percentage) are presented in descriptive analyses. The Shapiro–Wilk test was used to confirm normal distribution of the values. Welch Two Sample t-test and Fisher's exact test were used as appropriate for group comparisons.

To compare the primary and secondary outcomes, an unadjusted logistic regression was used. For the adjusted comparison a mixed model regression with random slope and binal user heparin was used as fixed effect. As postmenstrual age (PMA) and weight at PICC insertion are closely related, only weight at PICC insertion was used as random effect. Additionally, the number of catheter per infant was added as random effects to the mixed model.

PICC dwell times were compared using a Kaplan Meier survival analysis with censoring (mode of removal) and the cox-regression, with weight at PICC insertion and number of catheter per infant as confounding variables.

All statistical calculations were performed using the R-Statistics Software version 4.4.1 (The R Foundation for Statistical Computing, Vienna, Austria) with the CRAN-packages ggplot (v3.5.1), gtsummary (v2.0.3), lme4 (v1.1–35.5), survminer (v0.4.9), survival (v3.6–4) and consort (v1.2.2).

P-values <0.05 were considered as statistically significant.

2.5. Ethical statement

The study was approved by the ethical board in Stockholm (Dnr 2020-00260). Consent was not asked to each individual, since it was a retrospective study within the framework of clinical practice development and only anonymized data were used and presented in the analyses.

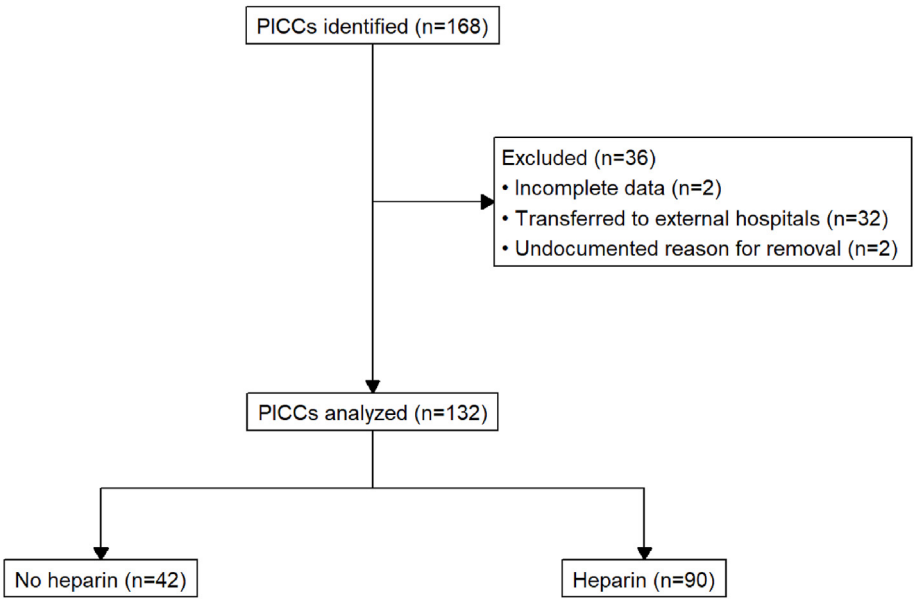

Fig. 1. CONSORT flow chart.

3. Results

3.1. Cohort

Out of 168 identified PICCs, 32 infants were transferred to hospitals with the catheter in situ, with no information about dwell-times and mode of removal available. Two PICCs had insufficient information in the records and two had no reason for removal documented, leaving 132 PICCs for analysis. Out of 132 eligible PICCs 90 were used with heparin containing nutrition admixtures (HG) and 42 without heparin, serving as control group (CG) (Fig. 1).

PICCs in the HG, showed both lower birth weight (median [IQR] 753 g [568, 932] vs 1,051 g [909, 1375]) and gestational age (GA) (25.3 vs 28.4 weeks) at birth. In both groups, the PICCs were inserted at the 7th day of life (median), but postmenstrual age (PMA) and weight at insertion day were significantly lower in the HG. Dwell times did not differ significantly between the groups with median [IRQ] 10 [6, 17] and 8 [5, 12] days, in the HG and CG, respectively. In the CG indication for PICC insertion was in all cases the need of parenteral nutrition. One PICC in the HG was exclusively used for medication, and all the others were exclusively or in combination used for parenteral nutrition. In addition, PICCs were used for administration of inotropic drugs in 12 (13 %) vs 2 (4.8 %) cases and other medication in 82 (91 %) vs 31 (74 %) cases, in the HG and CG respectively. No significant differences for other parameters could be found between the groups and can be obtained from Table 1.

3.2. Primary outcome

Catheters in the HG were exposed to heparin in median (IRQ) 91 % (73 %, 100 %) of the total dwell time. Sixty-six and 30 PICCs could be removed electively in the HG and the CG, respectively. The odds ratio (OR) for elective removal did not show any superiority between the groups (OR 95 % CI, 0.91 [0.41, 2.10], $p = 0.8$) which persisted after adjustment for weight at the time of insertion and the number of PICCs per infants (aOR 95 % CI 0.95 [0.31, 2.89], $p > 0.9$).

3.3. Dwell-times

The PICCs in the HG were used for in median [IQR] 10 days [6,17] and in the CG for 8 days [5,12] with no significant difference between the groups ($p = 0.11$). The last PICC was eliminated after 45 days and 46 days in the HG and CG, respectively (Fig. 2). In the cox regression analysis, the weight at PICC insertion had the strongest effect ($p = 0.056$) on the dwell-time model, but the difference remained insignificant with an HR 0.7 [95 % CI 0.45,1.09] $p = 0.11$.

3.4. Catheter related complications

Complications occurred in 17 (19 %) and 8 (19 %) PICCs in the HG and CG, respectively.

CLABSI occurred in four PICCs in the HG and two in the CG. Mechanical complications were documented in 7 (7.8 %) versus 4 (9.5 %) PICCs in the HG and CG. Vessel related complications, e.g. phlebitis, but not thrombosis, occurred in 6 (6.7 %) vs 2 (4.8 %) of the PICCs, respectively. Eight PICCs in the HG were removed postmortem.

There were no statistical differences in terms of catheter related complications between the groups in the unadjusted and adjusted analysis (Table 2).

4. Discussion

In this retrospective study we aimed to elucidate the effect of prophylactic heparin in PICCs on clinical important outcomes. In our population of PICCs inserted during one year att two level III NICUs in Stockholm, heparin did not ameliorate the elective removal rate at the end of the treatment period. Furthermore, the catheter associated complication rates, including catheter associated infections, were equally distributed using prophylactic heparin or not. Dwell-times did not differ between wether prophylactic heparin was used or not.

In our study, heparin did not alter the odds of elective PICC removal. These findings are in line with the results of two randomized controlled trials who did not find a difference in catheter occlusions and the rate of elective/planned PICC removal between the groups [4,6]. In a before-and-after implementation study,

Table 1
Cohort description, grouped by the use of heparin.

Characteristic	Overall, N = 132[a]	Control group, N = 42[a]	Heparin group, N = 90[a]	p-value[b]
Birth weight	870 (662, 1149)	1051 (909, 1375)	753 (568, 932)	0.001
GA	26.4 (24.9, 28.4)	28.4 (27.0, 30.4)	25.3 (24.3, 27.3)	<0.001
Anthropometry				0.088
AGA	104 (79 %)	30 (71 %)	74 (82 %)	
LGA	2 (1.5 %)	2 (4.8 %)	0 (0 %)	
SGA	26 (20 %)	10 (24 %)	16 (18 %)	
Insertion day (DOL)	7 (4, 10)	7 (3, 16)	7 (4, 10)	0.8
PMA on insertion day	28.0 (25.5, 30.0)	29.0 (28.0, 32.0)	27.0 (25.0, 29.0)	<0.001
Weight on insertion day	920 (675, 1279)	1199 (930, 1500)	758 (611, 1137)	0.002
Dwell time (days)	9 (6, 16)	8 (5, 12)	10 (6, 17)	0.12
Final tip location				0.8
Central	94 (71 %)	29 (69 %)	65 (72 %)	
Intermediate	20 (15 %)	6 (14 %)	14 (16 %)	
Peripheral	18 (14 %)	7 (17 %)	11 (12 %)	
Mode of elimination				0.8
Elective	96 (73 %)	30 (71 %)	66 (73 %)	
Non-Elective	36 (27 %)	12 (29 %)	24 (27 %)	
Number of PICC per infant				>0.9
1	99 (75 %)	33 (79 %)	66 (73 %)	
2	25 (19 %)	7 (17 %)	18 (20 %)	
3	6 (4.5 %)	2 (4.8 %)	4 (4.4 %)	
4	1 (0.8 %)	0 (0 %)	1 (1.1 %)	
6	1 (0.8 %)	0 (0 %)	1 (1.1 %)	
Dwell time with heparin (%)	0.76 (0.00, 1.00)	0.00 (0.00, 0.00)	0.91 (0.73, 1.00)	
Indication nutrition	131 (99 %)	42 (100 %)	89 (99 %)	>0.9
Indication inotrophic drugs	14 (11 %)	2 (4.8 %)	12 (13 %)	0.2
Indication other drugs	113 (86 %)	31 (74 %)	82 (91 %)	0.015
Complication				
Any complication	25 (19 %)	8 (19 %)	17 (19 %)	>0.9
CLABSI	6 (4.5 %)	2 (4.8 %)	4 (4.4 %)	>0.9
Mechanical	11 (8.3 %)	4 (9.5 %)	7 (7.8 %)	0.7
Vessel related harm	8 (6.1 %)	2 (4.8 %)	6 (6.7 %)	>0.9
Postmortem removal	8 (6.1 %)	0 (0 %)	8 (8.9 %)	0.055

CLABSI - Central line associated blood stream infection, DOL - Day of life, GA - Gestational age, PMA - Postmenstrual age, DOL - Day of life, PICC - Peripherally inserted central line.
[a] Median (IQR); n (%).
[b] Welch Two Sample t-test; Fisher's exact test.

occlusion rates did not differ when comparing 189 heparin exposed PICCs to 188 controls [8]. Tang et al. published the results from their retrospective trial only in Chinese, but calculating the difference from their abstract using a chi-square-test showed no significant difference in occlusion rates between the groups [11]. In contrast to these findings, the multicenter randomized controlled trial by Shah, and the single center controlled trials by Uslu and Klenner et al. demonstrate an increased rate of elective PICC removals and decreased odds for occlusions when using heparin in admixtures or infused separately [5,9,12].

Dwell-times in our cohort did not differ, which is in contrast to the findings reported by Shah, Klenner and Oslu [5,9,12]. The length of PICC usage, before elective removal, is not solely based on the catheter patency, as other factors may determine dwell-times, e.g. gestational age or medication with longer intended use. This could be confounding factors eventually interacting with the dwell-times even in the previously published studies. In our cox regression analysis, the weight at the time of PICC insertion had the strongest effect on the dwell-time model, suggesting a possibly significant effect on the dwell-times in a lager population.

Complication rates in our analysis were comparable to the complication rates reported by Isemann et al. and occurred in one out of five PICCs independent of whether prophylactic heparin was used or not [8]. In our cohort, CLABSI rates were generally low, and we were not able to find differences between the groups. In contrast, the studies by Tang and Birch reported a significant reduction of catheter associated infections in their heparin groups [4,11]. The studies by Kamala, Isemann, Shah and Uslu did not find any difference in infections between the groups [5,6,8,9]. Theoretically, a biofilm on the catheter and a thrombus could serve as starting point for microbial colonization and consecutive infection. The absence of thrombosis in our cohort could explain the low numbers of CLABSIs, making it impossible to determine the effect of heparin on infections [2]. Also, the small sample size in all studies, needs to be taken into account, making it impossible to determine the risk difference of complications between the groups.

In our study, heparin was added to the amino acid and glucose part of the parenteral nutrition admixture and co-infused with the fat components during administration. Uslu and Shah et al. infused heparin via a co-infusion while the other authors added heparin to a lipid including admixture [4,6,8,11,12]. A small number of studies have shown, that adding heparin to lipid emulsions can result in droplet forming and destabilization of the infused admixture and is therefore highly discouraged [13–15].

In contrast to a recent systematic review, our data could not demonstrate an advantage of heparin usage to maintain the usability of PICCs until their planned removal [7]. Our data could substantiate the ESPGHAN recommendation not to use heparin due to lack of evidence and potential hazardous side effects [2].

4.1. Strength and limitations

The strength of this study is the high number of analyzed PICCs with well documented outcomes. Furthermore, due to a robust

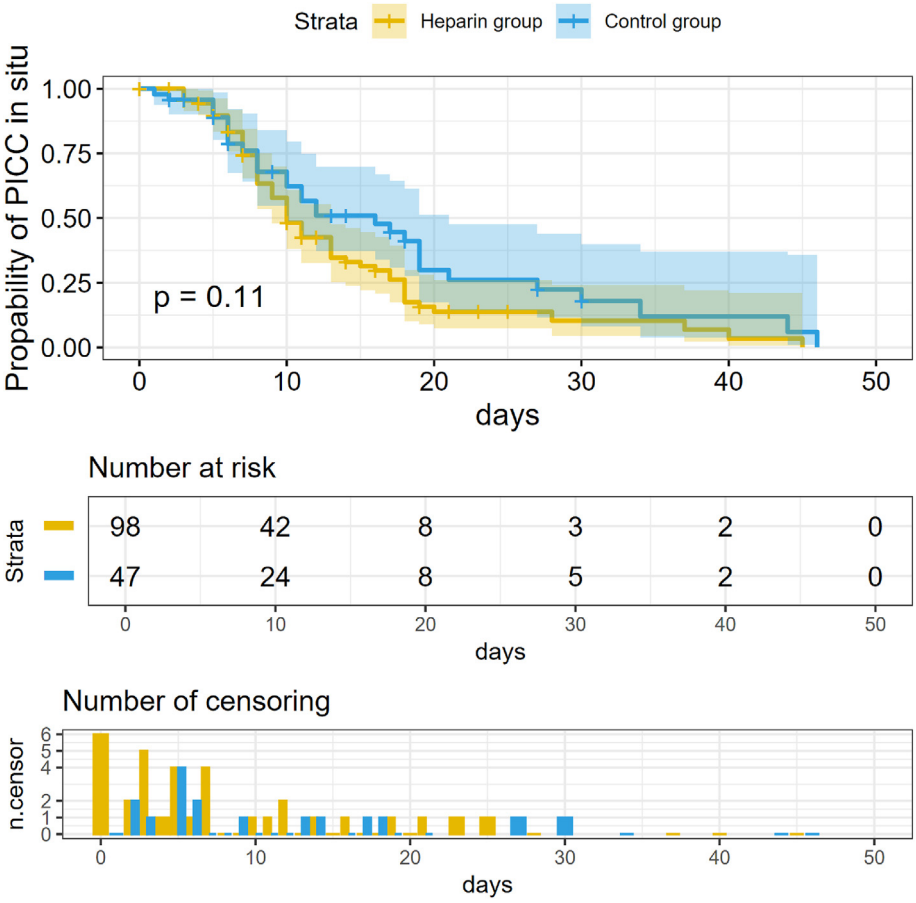

Fig. 2. PICC dwell-time, grouped by prophylactic heparin use.

Table 2
Comparison of PICC related complications.

Complications	OR	95 % CI	p-value	aOR[a]	95 % CI	p-value
Any	0.99	0.40, 2.63	>0.9	1.21	0.48, 3.02	0.7
CLABSI[b] (n = 6)	0.93	0.08, 6.91	>0.9	1.52	0.08, 27.2	0.8
Mechanical complications (n = 11)	0.80	0.23, 3.21	0.7	0.70	0.05, 9.99	0.8
Vessel related harm[c] (n = 8)	1.43	0.31, 10.0	0.7	2.18	0.52, 9.20	0.3

[a] Mixed regression model with use of heparin as fixed effect and weight at the time of PICC insertion and number of PICC per infant as random effects.
[b] CLABSI - Central line associated blood stream infection.
[c] Including phlebitis, but not thrombosis.

analysis using the mixed model approach, we were able to correct our model for potential confounding factors. Even a matched analysis with GA and weight on insertion day as matching variables, did not reveal a difference between the groups for both outcomes (Analysis not shown).

One of the limitations is the single center, retrospective chart review method used in this study, as both NICUs were within the Karolinska Neonatal department. Additionally, we were not able to collect exact data of heparin doses, which would have added more interesting aspects to our study. We did not use ultrasound to determine thrombosis at the catheter tip at the time of elimination regularly, which limits the informative value about this aspect.

5. Conclusion

Results from this case control study of prophylactic heparin usage showed no advantage in terms of elective removal, mechanical and infectious complications of PICCs in preterm and term infants. Furthermore, we were not able to find a difference in dwell-times between the groups. This study adds more evidence to the ESPGHAN recommendation, not to use prophylactic heparin in PICCs, omitting a potential hazardous drug in this highly vulnerable patient group.

Adequately powered randomized controlled trials are desirable to answer this clinical highly important question to possibly omit unnecessary drugs in this vulnerable patient group.

Authors contribution

D. Wackernagel: Conceptualization, Methodology, Validation, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision; V. Gavelli: Conceptualization, Validation, Investigation, Writing - Review & Editing; P. Nydert: Conceptualization, Methodology, Writing - Review & Editing, Supervision.

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Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2025.03.024.

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