ARTICLE

# Efficacy and safety of Low Dose Heparin infusion in intravenous fluids to prevent Peripherally Inserted Central Catheter (PICC) line occlusion among neonates: A Randomized Control Trial

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**OBJECTIVES:** To determine the efficacy of low-dose heparin in preventing central catheter occlusion and its safety among neonates.

**MATERIALS AND METHODS:** A randomized controlled trial was conducted among 42 neonates requiring peripherally inserted central catheter **(**PICC) lines. The neonates were divided into two groups: low dose heparin (0.5 units/kg/hr =0.2 units/ml) and control group (0.5 units/ml). The efficacy outcomes were duration of catheter patency, completion of catheter use, and the presence of catheter occlusion or thrombosis. The safety outcomes include heparin complications.

**RESULTS:** The study participants had a mean age of 17 days old at 35 weeks gestational age and mean weight of 1.97 kg. The participants given low dose heparin were 36% more likely to complete the use of central line and 12% less likely to develop catheter occlusion. Analyses showed non-statistically significant risk ratio of active bleeding, thrombocytopenia, and deranged prothrombin time in the low dose heparin group.

**CONCLUSION:** The use of low dose heparin (0.5 units/kg/hr = 0.2 units/ml) appears as effective as the control dose in completion of catheter use and prevention of catheter occlusion. There was also no significant difference in the adverse effects. Low dose heparin can be used as continuous infusion for preventing central line occlusion; however, it has no advantage in lowering the risk of complications.

**KEYWORDS:** *Peripherally Inserted Central Catheter (PICC), unfractionated heparin, occlusion, bleeding*

## INTRODUCTION

Most neonates in the Intensive Care Unit require intravenous lines for the administration of antibiotics as well as for continuous fluids. Peripheral venous line insertion is an easy procedure however its major disadvantage is its limited dwelling time which would require frequent change in site after 3-5 days. . [10] In comparison to peripheral lines, central venous lines or central venous catheters serve as an access for high osmolar drugs and prolonged total parenteral nutrition. There are several central lines available but the most used in our institution are the umbilical vein catheter (UVC), tunneled catheter and peripherally inserted central catheter (PICC). The PICC lines are now frequently used because they serve as a stable, long-lasting access which may last for four weeks.

The presence of central venous catheters aids in providing optimal care among our neonates hence maintaining its patency is of utmost importance. There are several risk factors that may contribute to central line occlusion and lead to its early removal. Common complications include occlusion (15-48%), thrombosis (25%) and phlebitis (7.5%).[10] Newborns have increased risk for thromboembolic events among the pediatric group due to low levels of antithrombin III and may have a higher incidence of catheter occlusion. Heparin is a popular anti-coagulant with its action mediated through the activation of antithrombin III in the plasma. It is widely used for maintenance of intravascular access due to its rapid action and lower cost.[13]

Literature recommends the use of continuous heparin to prolong the use of central lines as documented in a systematic review on prophylactic use of heparin in central lines as studied by Bin-Nun et al. Most studies on continuous heparin infusion compared its efficacy in maintaining central line patency with a placebo or saline solution. In a study by Kamala et al., the use of continuous heparin infusion prolongs catheter patency by three days in comparison to no heparin. A meta-analysis of randomized controlled trials was done locally by Ilagan et al., which showed that continuous heparin infusion in PICC prolongs duration of catheter patency by two days. In these studies, varying heparin doses were used from 0.5 units/kg/hr (0.2units/ml) to as high as 1unit/ml. In the 9th American College of Chest Physicians consensus conference, they recommended the use of unfractionated heparin at 0.5units/kg/hr as continuous infusion in central lines. Recent studies by Birch et. al (2010) and Tang et al. (2011) showed that the use of heparin at a higher dose (0.5units/ml) decreases catheter occlusions hence prolongs catheter patency duration compared to no heparin administered. Locally, we have adopted the higher heparin dose at 0.5units/ml as continuous infusion in our neonatal intensive care unit (NICU) to maintain our PICC lines. Limited studies have been done comparing heparin doses in terms of efficacy and safety since most heparin studies has been compared to placebo or no heparin group. A comparison of two doses, like our study, was done by Barekatain et al. comparing a low dose heparin (1.5unit/kg/hr) and a higher dose heparin (0.5units/ml). The same outcome measures such as duration of catheter time and catheter occlusion were observed and revealed that a lower dose heparin is as effective as that of the higher dose in maintaining the patency of the PICC line.

Despite this, the benefits versus harm of heparin use in central lines are cautiously weighed. Considering the heparin doses that have been studied, it would be prudent to compare the lowest heparin dose (0.5 units/kg/ hr = 0.2units/ml) proven to prevent catheter occlusion with that of the current heparin dose (0.5 units/ml) being used. In line with this, the determination of a lower heparin dose may decrease the associated risk to the patient. This study aims to determine the efficacy of a low dose heparin in intravenous fluids to prevent central line occlusion. The specific objectives of the study are as follows: (a) To compare the

efficacy of heparin concentrations (0.5 units/kg/hr=0.2units/ml and 0.5 units/ml) in mean central line patency duration, proportion of completed use of central line and catheter occlusion; (b) To compare incidence of adverse effects such as significant thrombocytopenia (less than 100,000), deranged prothrombin time, intraventricular hemorrhage or any form of bleeding among two different doses.

## Materials and methodology

A randomized controlled trial was done to study the efficacy of a lower dose unfractionated heparin (0.5 units/kg/hr = 0.2units/ml) compared to conventional dose in preventing catheter occlusion of peripherally inserted central catheters (PICC). Single blinding and allocation concealment were done.

The study included all neonates with peripherally inserted central catheters (PICC) used for administration of intravenous fluids and antibiotics. Neonates who required reinsertion of PICC line were included as a separate group. Neonates with clinical evidence of bleeding, thrombocytopenia (less than 100,000), IVH grade 3 or 4, and prolonged PT, PTT were excluded.

The sample size was initially computed at 70 study participants using independent *t*-test for two sample proportion. In the last three months of the study, there was an unexpected closure of the Neonatal Intensive Care Unit (NICU) due to an increasing rate of infection. This caused a decrease in number of admissions and affected data collection. A post-hoc power analysis for One-Way Multivariate Analysis of Variance (MANOVA) was conducted using GPower version 3.1.9.4 to compute for the adequacy of sample size reached within seven months of the study. With three outcomes, two group categories, and an accumulated sample size of 42 participants, multivariate analysis estimated a partial eta squared ($\eta^2$) of 0.090 which can be utilized to compute for effect size *f* of 0.3145. With these estimates from the collected data, the acquired sample of 42 participants was sufficient to achieve a power of 93.11%.

The study included all neonates of a tertiary government hospital who required peripherally inserted central catheters (PICC) line for intravenous fluids including total parenteral nutrition (TPN) and antibiotics. Neonates who required re-insertion of a PICC line were included as well. A PICC line was inserted by a physician at the NICU following a sterile technique. The catheter size and insertion site were determined by the attending physician. The catheters used were Vygon French size 1 and French size 2.

The proper placement of the central line was evaluated with a radiograph. An informed consent was provided, and the study was explained to the parents of the participants. Once informed consent was secured, baseline workups such as complete blood count and prothrombin time were done prior to heparin and after 24 hours from heparin administration. A cranial ultrasound was done for those high risk for intraventricular hemorrhage. Neonates

with clinical evidence of bleeding, thrombocytopenia (less than 100,000), prolonged prothrombin time, and intracranial hemorrhage grade 3-4 were excluded.

The primary investigator prepared a randomization list. The group assignments were placed in sealed envelopes which were sequentially arranged. Once an eligible patient was encountered, the envelope was opened, and the group assignment of the participant was read. The participants were divided into two groups. The first group was the Control Group where heparin dose given to maintain central line patency is at 0.5units/ml (see Figure). The second group was the Intervention Group where heparin dose was at 0.5units/kg/hr (=0.2 units/ml). Both groups used unfractionated heparin (preparation 1000 units/ml, 5ml per vial) mixed with intravenous fluids and given via continuous infusion.

The primary investigator gathered the data of the study participants which includes the demographics, clinical data, and laboratories. Baseline demographics included were age, sex, gestational age, weight, type of catheter used, type of vein used, type of intravenous fluid (IVF), antibiotics being given and underlying medical conditions.

We computed for the heparin to be incorporated in the intravenous fluid including total parenteral nutrition and it was ordered in the chart. The chart order of the requested intravenous fluids was prepared by the pharmacist who is not part of the research group and does not do bedside rounds. Standard PICC line care was observed by the NICU staff for all study participants at all times: (a) the PICC lines were secured properly; (b) only 10ml syringes were used in administration of fluids and medications using the PICC lines and will be given via continuous infusion or via push-pause method; (c) extractions and insertions on the PICC line area were prohibited; (d) blood transfusion via PICC line was not allowed. The study participants and the duration of the PICC line patency was observed for one week to one month. The observation was set to a maximum of one month due to the recommended duration of PICC line use.

The primary outcomes included measured variables such as: (a) number or proportion of catheter occlusion; (b) number or proportion of completed use of central lines; and (c) mean duration of catheter use. Catheter occlusion is defined as the presence of any of the following (a) decrease or absence of flow through the central line, (b) erythema or swelling on the catheter site requiring prompt removal of the catheter or © presence of blood clot after removal of the catheter. The presence or absence of a blood clot or thrombus formation was documented by pushing 5ml of PNSS into the catheter after the central line has been removed. The number of completed use of central line is defined as the number of days from PICC line insertion to the day of completion of antibiotics and discontinuation of intravenous fluids. The duration of catheter use is defined as the number of days from the central line insertion to the removal of the catheter. The principal investigator made daily rounds in the morning and used a monitoring

sheet to observe for any sign of occlusion. The monitoring sheet was used to check for the PICC line status and if its removal is warranted. The PICC line was removed once noted with any signs of catheter occlusion. The presence of occlusion was confirmed by the principal investigator, co-investigator and one neonatology fellow. Secondary outcomes in the study are development of thrombocytopenia (less than 100,000), deranged prothrombin time, and any form of bleeding.

Heparin as a medication has its side effects which commonly presents with bleeding. Heparin was discontinued immediately among study participants with any sign of bleeding and derangement in the bleeding parameters however they were still included as part of the study for monitoring. The data of these participants were used to analyze the safety outcome of the study. The cranial ultrasound used for monitoring intraventricular hemorrhage was shouldered by the research funds among participants with high risk for bleeding. The study was approved by the Institutional Review Board – Independent Ethics Committee.

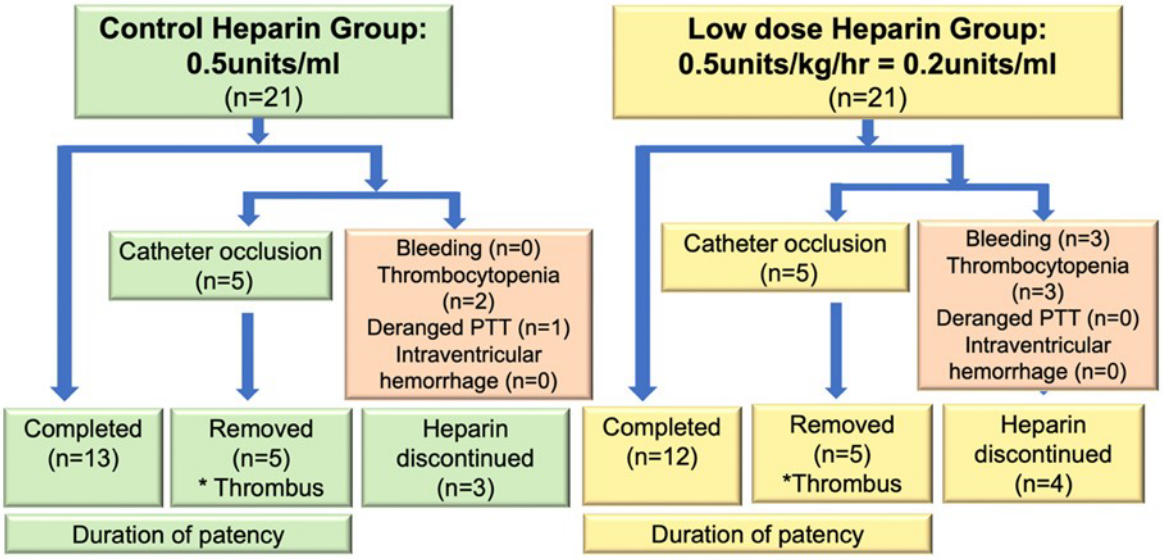


**Figure.** Study flow of neonates with PICC lines and outcomes on two different heparin doses given via continuous infusion

Statistical analyses were conducted using STATA Statistical Software, Version 13, College Station, TX: StataCorp LP. A *p*-value of 0.05 or less was considered statistically significant. Descriptive statistics included mean and standard deviation for continuous-level data, median and interquartile range for ordinal data, and frequency and proportion for nominal data. Comparative analyses of the demographic and clinical characteristics according to group allocation were conducted using Chi-Square Test of Homogeneity for nominal data or Fisher's Exact Test, if the expected frequency per cell is less than 5; Mann-Whitney U Test, for ordinal or non-normally distributed, continuous data; and, independent t-test for normally-distributed, continuous data. [17]

Between-group comparison of the duration of central line catheter patency was conducted using analysis of covariance, and the mean duration of patency was adjusted to significant confounders. [17] On the other hand, log-binomial regression using generalized linear model approach was performed to determine the relative risk of the outcomes (completed use of central line catheter, central line occlusion or thrombosis, active bleeding, thrombocytopenia, and deranged bleeding parameters) according to group assignment. Crude risk ratio (cRR) was initially estimated. Afterwards, significant confounders were screened, analyzed, and controlled using a 10% change-in-estimate criterion to estimate the adjusted risk ratio (aRR).[18]

## RESULTS

The study had a total of 42 participants who met the inclusion criteria. There were 21 participants in the control group (0.5 units/ml) and 21 participants in the low heparin group (0.5 units/ kg/hr =0.2units/ml). Seven were withdrawn due to complications such as bleeding and deranged laboratory results hence the discontinuation of heparin infusion. There were 2 deaths from those patients withdrawn from the study. Intention To Treat analysis was done to preserve the sample size and randomization of the study. No participant was lost to follow-up.

Table 1 illustrates the demographic and clinical characteristics of the participants. The mean age of the participants was 17.76 days old (SD=11.80). The mean gestational age and the corrected gestational age upon entry to the study were 35.62 weeks and 37.86 weeks respectively. Most of the participants were male (61.90%). The mean weight of the study in the low dose heparin group at 2.06 kilograms (SD 0.96) was higher compared to control group at 1.89kilograms (SD 0.90). French size 1 peripherally inserted central catheter (PICC) was commonly used and was frequently inserted in the cephalic vein for both groups. The PICC line was primarily used for total parenteral nutrition with lipid emulsion as well as administration of medications which were mostly antibiotics. The top three medications in the control group were meropenem (42.86%), fluconazole (33.33%) and vancomycin (28.57%). The top three medications in the low dose heparin group were meropenem (42.86%), amikacin (23.57%), vancomycin (19.05%) and fluconazole (19.05%). Table 1 also shows that the most common underlying medical condition for both groups was infection (80.95%). The other medical conditions common in the low heparin group are surgical cases (47.62%) followed by respiratory diseases (23.81%). In the control group, gastro-intestinal cases (52.38%) ranked as the second common condition followed by surgical cases (23.81%) and respiratory diseases (23.81%). Comparative analyses of the different demographic and clinical characteristics according to group allocation indicated that none of the demographic and clinical characteristics were significantly different between the two dosages of heparin.

**TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PARTICIPANTS ACCORDING TO GROUP ALLOCATION**

| Characteristics | Group Allocation (N = 42) | | | *p*-value (Two-Tailed) |
|---|---|---|---|---|
| | Low Heparin (n = 21) | Control (n = 21) | Total (N = 42) | |
| **Age (days old; x̄, SD)** | 20 (14.96) | 15 (7.04) | 17 (11.80) | 0.194 |
| **Corrected Age (weeks; x̄, SD)** | 38 (3.66) | 37(3.68) | 37(3.65) | 0.505 |
| **Gestational Age (weeks; x̄, SD)** | 35 (3.16) | 35 (3.68) | 35 (3.39) | 0.789 |
| **Sex (*f*, %)** | | | | 0.204 |
| *Male* | 11 (52.38%) | 15 (71.43%) | 26 (61.90%) | |
| *Female* | 10 (47.62%) | 6 (28.57%) | 16 (38.10%) | |
| **Weight (kilograms; x̄, SD)** | 2.06 (0.96) | 1.89 (0.90) | 1.97 (0.93) | 0.568 |
| **Size of Catheter (French; *f*, %)** | | | | 1.000 |
| *French Size 1* | 17 (80.95%) | 17 (80.95%) | 34 (80.95%) | |
| *French Size 2* | 4 (19.05%) | 4 (19.05%) | 8 (19.05% | |
| **Vein used for Catheter (*f*, %)** | | | | 0.915 |
| *Cephalic* | 10 (47.62%) | 12 (57.14%) | 22 (52.38%) | |
| *Basilic* | 4 (19.05%) | 3 (14.29%) | 7 (16.67%) | |
| *Tibial* | 1 (4.76%) | 0 (0.00%) | 1 (2.38%) | |
| *Saphenous* | 6 (28.57%) | 6 (28.57%) | 12 (28.57%) | |
| **Intravenous Fluids (*f*, %)** | | | | 1.000 |
| *TPN with Lipids* | 17 (80.95%) | 17 (80.95%) | 34 (80.95%) | |
| *TPN without Lipids* | 1 (4.76%) | 0 (0.00%) | 1 (2.38%) | |
| *Crystalloids* | 3 (14.29%) | 4 (19.05%) | 7 (16.67%) | |
| **Medications (*f*, %)** | | | | |
| *Antibiotics* | 19 (90.48%) | 18 (85.71%) | 37 (88.10%) | 1.000 |
| *Anti-Fungal* | 5 (23.81%) | 7 (33.33%) | 12 (28.57%) | 0.734 |

| | | | | |
|---|---|---|---|---|
| **Underlying Medical Conditions (*f*, %)** | | | | |
| *Infection* | 17 (80.95%) | 17 (80.95%) | 34 (80.95%) | 1.000 |
| *Respiratory* | 5 (23.81%) | 5 (23.81%) | 10 (23.81%) | 1.000 |
| *Cardiovascular* | 2 (9.52%) | 2 (9.52%) | 4 (9.52%) | 1.000 |
| *Surgical* | 10 (47.62%) | 5 (23.81%) | 15 (35.71%) | 0.197 |
| *Gastrointestinal* | 3 (14.29%) | 11 (52.38%) | 14 (33.33%) | 0.009 |
| *Neurologic* | 3 (14.29%) | 1 (4.76%) | 4 (9.52%) | 0.606 |

Significant at 0.05

†Significant at 0.01

The comparison of the efficacy outcomes between the two groups are presented in Table 2. Although the duration of central line patency was longer in the control group with higher heparin dose, this was not statistically significant. Results also indicated that the proportion of participants who had completed use of central line was slightly higher at 61.90% in the control group and 57.14% for the low dose heparin group, with an adjusted risk ratio of 1.36. Both groups had similar proportions of participants who had central line occlusion or thrombosis (23.81%), yielding an adjusted risk ratio of 0.78 (95% CI = 0.30 – 2.03), after adjusting for the confounding effect of duration of PICC use. The risk of central line occlusion or thrombosis was not statistically different between the two groups. Among the 23.81% of participants who had central occlusion, none of them had thrombosis upon catheter removal.

**TABLE 2. BETWEEN-GROUP COMPARISONS OF EFFICACY OUTCOMES AMONG THE PARTICIPANTS ACCORDING TO GROUP ALLOCATION**

| Efficacy Outcomes | Group Allocation (N = 42) | | | Mean Difference (95% CI) | Crude RR (95% CI) | Adjusted RR (95% CI) | *p*-value (Two-Tailed) |
|---|---|---|---|---|---|---|---|
| | Low Heparin (n = 21) | Control (n = 21) | Total (N = 42) | | | | |
| **Duration of Central Line Patency (Days; Adj. x̄, SD)** | 13.29 (6.19) | 16.81 (8.55) | 16.81 (7.58) | 3.52 (–1.13 – 8.18) | | | 0.112 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Completed Use of Central Line (*f*, %)** | 12 (57.14%) | 13 (61.90%) | 25 (59.52%) | 0.92 (0.56 – 1.52) | 1.36 (0.86 – 2.15) | 0.184 |
| **Central Line Occlusion (*f*, %)** | 5 (23.81%) | 5 (23.81%) | 10 (23.81%) | 1.00 (0.34 – 2.95) | 0.78 (0.30 – 2.03) | 0.610 |

[a]Note: Summary statistic for duration of central line patency is presented in mean difference, while it is adjusted risk ratio for completed use of central line and central line occlusion or thrombosis. The mean duration of central line patency and the risk ratios for completed use of central line and central line thrombosis or occlusion were adjusted to significant confounders (duration of PICC).

[*]Significant at 0.05

[†]Significant at 0.01

Table 3 depicts the comparison of safety outcomes among the participants according to group allocation. Among the 42 participants, seven had their heparin discontinued due to complications such as bleeding and deranged laboratory findings. Less than a quarter of the participants had thrombocytopenia (11.90%), active bleeding (7.14%), or deranged prothrombin time (2.38%). Among participants in the low heparin dose group, 14.29% had active bleeding, 14.29% had thrombocytopenia and none had deranged prothrombin time. On the other hand, 9.52% had thrombocytopenia, 4.76% had deranged prothrombin time and none had bleeding among those who were in the control group. Cranial ultrasound was done to those with high risk for bleeding and showed no intracranial findings. Analyses after adjusting for confounding effects of age and sex indicated that the adjusted risk of active bleeding, thrombocytopenia, and deranged prothrombin time were not statistically significant between the groups.

**TABLE 3. BETWEEN-GROUP COMPARISON OF SAFETY OUTCOMES AMONG PARTICIPANTS ACCORDING TO GROUP ALLOCATION**

| Safety Outcomes | Group Allocation (N = 42) | | | Crude RR (95% CI) | Adjusted RR (95% CI) | *p*-value (Two-Tailed) |
|---|---|---|---|---|---|---|
| | Low Heparin (n = 21) | Control (n = 21) | Total (N = 42) | | | |
| **Active Bleeding (*f*, %)** | 3 (14.29%) | 0 (0.00%) | 3 (7.14%) | 1.02 (0.98 – 1.01) | 2.63 (0.45– 15.25) | 0.280 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Thrombocytopenia (*f*, %)** | 3 (14.29%) | 2 (9.52%) | 5 (11.90%) | 1.50 (0.28 – 8.08) | 1.38 (0.90 – 2.72) | 0.752 |
| **Deranged Prothrombin Time (*f*, %)** | 0 (0.00%) | 1 (4.76%) | 1 (2.38%) | 1.03 (0.96 – 1.09) | 0.99 (0.98 – 1.01) | 0.994 |

[a]Note: Risk ratios were adjusted for the participant's Age and Sex.

[*]Significant at 0.05

[†]Significant at 0.01

## Discussion

In this study, 42 participants who underwent PICC line insertion were evaluated on the effectiveness and safety of low dose heparin (0.5units/kg/hr =0.2units/ml) in comparison to the control dose heparin (0.5units/ml). The mean gestational age and mean weight for both groups were 35 weeks and 1.94kg respectively. The PICC catheter frequently used was French size 1 due to its small diameter and smaller needle gauge introducer preferred for preterm and low birthweight patients. The size of the catheter would also depend on the visualized vein appropriate for PICC line insertion. The basilic vein is said to be a good site for its large diameter and less tortuosity, however, prior to insertion of the catheter all possible veins must be examined. In this study, the cephalic vein was the most common insertion site. The PICC line as a central access has been very helpful in providing adequate nutrition to our high-risk neonates in the form of Total Parenteral Nutrition (TPN) with accompanying lipid emulsion which is known for its high osmolality.

The most common underlying medical condition in the study was infection (80.95%) which is mostly sepsis or blood infection (54.76%) followed by pneumonia (30.95%). The organism commonly seen positive in the blood culture was *coagulase negative Staphylococcus* (CONS). These organisms are usually part of the normal skin flora however they can also become opportunistic organisms and frequently cause nosocomial infections among high-risk neonates.[25] PICC lines were of great importance to the completion of the medications, particularly the antibiotics (88.10%) for the treatment of infection in both

groups. It can be noted that the antibiotics frequently used for both groups were broad spectrum used for serious infections. The presence of sepsis is a significant risk factor affecting the efficacy and safety of heparin in the study. Presence of inflammation causes elevation of the acute phase reactants which may lead to increased blood viscosity and aggregation of erythrocytes. Blood viscosity promote fibrin and thrombus formation causing catheter occlusion. [21] On the other hand, sepsis may also lead to decreased platelet or thrombocytopenia.[22]

Thrombus formation is highly related to the Virchow's triad of endothelial damage, stasis and state of hypercoagulability which may occur in neonates with dehydration, asphyxia and polycythemia. [23] The presence of the other underlying medical conditions such as in surgical cases, gastrointestinal and cardiovascular diseases may increase risk for occlusion due to their hypercoagulable state. [23] Overall, the statistical analysis based on the demographics and clinical characteristics of both groups showed no significant difference hence they are comparable with each other.

Heparin is an anti-coagulant which inactivates factor Xa and thrombin. Higher doses of heparin prevent thrombus formation and fibrin conversion therefore helps in maintaining catheter patency.[1] The mean duration of central line patency in the study was not statistically significant but was noted to be three days longer in the control group with higher heparin dose (0.5units/ml). This difference in the duration of catheter patency of three days, however, may be considered of clinical importance particularly in the completion of fluids and medications.

This contrasts with the study by Barekatain et al., the mean duration of catheter patency in the low heparin dose (1.5units/kg/hr) and higher heparin dose (0.5units/ml) were 15.5 days and 14.6 days respectively which showed no significant difference in both groups.

More than half of the participants completed the use of the central line. Twelve participants from the low dose group (57.14%) and 13 (61.90%) from the control group completed use of the central line. Based on the adjusted risk ratio of 1.36, the study participants who received low dose heparin were 36% more likely to complete the use of central line. In terms of catheter occlusion, similar proportion of participants was noted with 5 (23.81%) participants each group. The adjusted risk ratio of 0.78 showed that study participants receiving the low dose heparin were 12% less likely to develop catheter occlusion. There was no thrombus formation noted after saline solution flushing of the catheter upon removal. The risk of completed use of central line, and the risk of central line occlusion or thrombosis were not statistically different between the two groups as well. This indicates that continuous infusion of low dose heparin (0.5units/kg/hr =0.2units/ml) may allow completion of catheter use and prevention of catheter occlusion.

Most studies on the use of continuous heparin infusion in maintaining catheter

patency and prevention on occlusion were done using different doses of unfractionated heparin and its effect was compared to placebo or no heparin group. In a study by Uslu et. al., a decrease in the PICC occlusion was noted in the heparin group at 0.5units/kg/hr (19.5%) as compared to no heparin group (45.5%). Another study with the same outcomes was done by Shah et. al. which also showed lower PICC line occlusion rate (6%) in the heparin group at 0.5units/kg/hr in comparison to the group without heparin (31%). Similar to the study by Barekatain et al., more than half of the study participants in both the high dose heparin at 0.5units/ml (58.5%) and low dose heparin at 1.5units/kg/hr (60.4%) completed treatment or central line use. The proportion of study participants with catheter occlusion presenting with lack of patency showed to be the same in both groups as well, 26.4% in the high dose heparin while 22.6% in the low dose heparin. The study by Barekatain et al. concluded that there was no significant difference in the efficacy of the two doses hence the use of low dose heparin (1.5units/kg/hr) in maintaining catheter patency and preventing catheter occlusion is as effective as the high dose heparin.

Newborns have increased hepatic clearance of heparin and a half-life of one to three hours hence the need for a higher heparin dose to achieve therapeutic level. [1] Heparin as a medication may cause adverse effects particularly of hematologic concerns. They may present with overt bleeding, significant thrombocytopenia (less than 100,000) or elevated activated prothrombin time (aPTT) based on age. It may be assumed that an increase in risk for complications may be expected with a higher heparin dose. In general, the most common complication noted in the study was thrombocytopenia (11.90%). In the low dose heparin group, bleeding and thrombocytopenia were frequently noted (14.29%). It is important to know that two study participants with active bleeding were also noted to have thrombocytopenia. There were two participants who had thrombocytopenia (9.52) and only one had a deranged prothrombin time in the control group. There was no case of intraventricular hemorrhage noted in the cranial ultrasound of the study participants. Study participants with low dose heparin (0.5units/kg/hr =0.2units/ml) had 263% higher risk for active bleeding and 36% higher risk for thrombocytopenia but these were not statistically significant. Similar to the findings in the study by Uslu et.al.,the use of low dose continuous heparin (0.5units/kg/hr) was not associated with complications such as thrombocytopenia, prolonged aPTT, septicemia and intracranial hemorrhage. Heparin incorporation has been discontinued upon recognition of any complication in the study participants. No participant was noted to have complications that was proven to be secondary to heparin alone because the presence of other risk factors such as infection is highly significant. In the presence of sepsis, bleeding may be observed secondary to thrombocytopenia. About 50% of patients with

sepsis would present with thrombocytopenia due to decreased platelet production or increased immune mediated platelet destruction. The activation of platelets occurs in response to coagulation and inflammatory cascades. [26] It is of great importance to note that the participants with complications particularly those with active bleeding also had concurrent sepsis with identified growth in their blood cultures. The two common blood culture isolates were coagulase negative *Staphylococcus* and *Acinetobacter baumanii.* Both gram positive and gram-negative organisms may have direct interaction and activation of the platelets which may affect its production and destruction. Platelets function by aggregating in the endothelial damage hence its depletion may lead to bleeding.[26] The complications in the use of low dose heparin (0.5units/kg/hr =0.2units/ml) were statistically non-significant. However, low dose heparin showed no significant decrease in the risk for complications in comparison to the control group.

## Conclusions

The use of low dose heparin (0.5units/ kg/hr =0.2units/ml) appears as effective as the control dose (0.5units/ml) in completion of catheter use and prevention of catheter occlusion. There was also no significant decrease in the risk for complications in the low dose heparin. Low dose heparin can be used as continuous infusion for preventing central line occlusion however it has no advantage in lowering the risk for complications.

The sample size of the study was limited due to increased infection rate prompting sudden closure of the Neonatal Intensive Care Unit. The small sample size highly affected the confidence interval which showed a wide range and may indicate a less precise estimate.

Low dose heparin infusion may be considered as part of our NICU policy in maintaining PICC line patency. Further studies may be done comparing the efficacy and safety of several doses. Studies on relationship of heparin and sepsis may also be recommended since infection has been an important factor in this study.

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