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Intermittent heparin is not effective at preventing the occlusion of peripherally inserted central venous catheters in preterm and term neonates

Heparina intermitente não é eficaz em impedir a retirada por obstrução de cateteres centrais inseridos perifericamente em recém-nascidos de termo e prematuros

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ABSTRACT

Objective: To evaluate the effectiveness of intermittent 10 U/mL heparin flushes in reducing the occlusion of peripherally inserted central catheters in neonates.

Methods: In this randomized, open-label, prospective, controlled study, neonates were allocated either to receive 0.5 mL flushes of heparin (Group 1: n = 64) or saline (Group 2: n = 69) every 4 hours. Actions were taken to restore patency by using negative pressure (3-way stopcock method) in cases of occlusion.

Results: A total of 133 neonates were included. No significant intergroup difference was observed in the number of new occlusions (26 in Group 1, or 31/1,000 catheter-days; 36 in Group 2, or 36/1,000 catheter-days; P = 0.19). In Group 1, 5 catheters had 9 recurrent obstructions after successful clearance maneuvers. In Group 2, 19 catheters had 40 relapses (P < 0.0001), showing heparin's protective role against recurrence of obstruction (Relative Risk = 0.36). However, heparin failed to prevent catheter withdrawal due to permanent occlusion (3 catheters in Group 1 and 8 in Group 2; P = 0.24).

Conclusion: Intermittent heparin is not effective for preventing the occlusion of peripherally inserted central catheters in neonates but reduces relapses when clearance maneuvers were successful.

Keywords: Heparin; Infant, newborn; Critical care; Nursing care; Catheters, indwelling

Study conducted at Hospital Santa Marina – São Paulo (SP), Brazil.

Conflicts of interest: None.

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INTRODUCTION

Peripherally inserted central catheters (PICCs) have become essential for neonatal intensive care because it prevents newborns from having to undergo multiple painful punctures. In addition, it provides safe and continuous venous access.[1] However, these are not complication-free devices. In addition to the risks of infection and thrombosis that are inherent with any intravenous device, an occlusion may lead to a catheter loss, which requires an interruption of therapy and potentially results in new traumatic punctures that impair the quality of assistance. Factors contributing to occlusion include the catheter material and gauge, the infused solution, the connectors, the unit-specific handling protocols as well as various patient-related aspects (such as hypercoagulability states).[2] Obstructions due to fibrin and blood components (thrombotic occlusion) are more common. Other non-thrombotic causes may include mechanical issues, such as tight sutures, inappropriate placement and folding. Obstructions may also result from the precipitation of infused components (e.g., calcium and phosphorus

precipitate during parenteral nutrition therapy) or lipid condensations.[3]

Measures to prevent thrombotic occlusions include frequent catheter flushes and additional precautions to prevent blood refluence. For many years, because of heparin's anticoagulant properties, physicians have prescribed catheter flushes and filling with heparin, with no clear benefits. Few studies have focused on the clarification of heparin's role in the effective prevention of occlusions, and studies that have been conducted on this subject have yielded conflicting information due to inappropriate samples and inconsistent methodologies.[4,5] In 2007, however, Shah et al. clearly showed that continued heparin infusions prolonged the useful life of PICCs in newborns.[6]

The use of intermittent PICC flushing with heparin is not evidence-based, as no studies with appropriate methodology have been conducted. This controlled, randomized trial was designed to evaluate whether intermittent (every 4 hours) low-dose heparin (10 U/mL) flushes were more effective than saline flushes for the maintenance of patency and the extension of the useful life of PICCs in newborns. As secondary endpoints, we assessed the safety of this mode of heparin administration to newborns by surveillance of bleedings, low platelet counts or intracranial bleedings.

METHODS

This study was conducted at the Neonatal Intensive Care Unit (NICU) of a tertiary hospital in São Paulo, Brazil from June 2006 to August 2007. The study protocol was approved by the institution's Ethics Committee under protocol #02/2006, and for each child, an informed consent form was signed by one or both parents. All newborns with an indication for PICC insertion whose parents consented to participation in the study were eligible for this trial. Additionally, we required that the catheter location be central and extra-cardiac (at the superior vena cava, confirmed by radiographic imaging). Peripherally located catheters, coagulopathies, low platelet counts (below 150,000), clinical and/or ultrasound signs of intracranial hemorrhage and lack of parental consent were the exclusion criteria.

Silicone Becton & Dickinson (BD First Picc®) 1.9 French catheters with a peel-away Introsyte® sheath were used. The preferred veins for puncture attempts were the basilic, cephalic and median cubital, in that order. Commercial heparin (sodium heparin 5,000 IU/mL) was diluted with saline solution to obtain 10 U/mL. Trained nurses working in the unit were responsible for the insertions using standard sterile techniques. The catheters were handled with an aseptic technique by nursing technicians and nurses, and for all catheters, needleless connectors were used (Clave®, Abbott). Data related to the insertion, persistence time, demographics, type of catheter, time of infusion with infusion pump, obstructions, breakings, ruptures, leakages, phlebitis and other complications and intercurrent events were recorded on specific forms.

Randomization was performed using specific software (Research Randomizer http://www.randomizer.org). Because this was a prospective, open-label trial, the patients were randomized in the Neonatal Intensive Care Unit (NICU) and were assigned to one of the study groups according to the randomization list immediately after the catheter insertion. Patients assigned to Group 1 had their PICC flushed with 0.5 mL heparin 10 U/mL every 4 hours using 10 mL syringes, and patients in Group 2 had their PICC flushed with 0.5 mL saline every 4 hours.

Occlusion was characterized as the inability to inject 1 mL saline through the catheter without resistance; when occlusion occurred clearance maneuvers were required. If patency was recovered, the occlusion was categorized as 'non-permanent'. 'Permanent' occlusions were those that could not be resolved within 24 hours of attempted clearance; in these cases, the catheters were withdrawn. Clearance was attempted using negative pressure maneuvers as originally described for urokinase and alteplase administrations[7] (3-way stopcock method). The negative pressure maneuvers were performed by connecting a three-way tap to the catheter, after which two 10 mL syringes were connected to the tap, one filled with 5 mL clearance solution (heparin 10 U/mL in Group 1, saline in Group 2) and the other one empty. The catheter's content was suctioned using the empty syringe, causing a vacuum, and then this access was closed. The access with the syringe containing the clearance solution was then opened to fill the catheter with the suctioned volume of clearance solution. The system was kept closed and tested with blood refluence at 5 minutes, 10 minutes and then every 30 minutes up to 24 hours. The catheter was categorized as cleared when 1 mL saline could be freely infused with a 10 mL syringe with no resistance, or blood refluence.

Although the heparin doses were low and unlikely to cause changes in coagulation, routine ultrasound imaging tests, requested by the treating physician, were

evaluated for intracranial hemorrhages and categorized according to Papile's scoring system.[8] Blood count and coagulogram tests were monitored for low platelet counts and coagulation markers. The main indications for central venous access were the need for parenteral nutrition (PNT), prolonged antibiotic therapy due to sepsis and the use of vasoactive drugs. Sepsis was defined as one or more specific conditions, including respiratory distress, gastrointestinal symptoms (vomiting, abdominal distension), temperature lability, hypotension, metabolic acidosis, hyperglycemia, lethargy, seizures, bleedings), combined with low white blood cell counts (< 5,000 white blood cells/μL),[8] left shifted leukocytosis, low platelet counts or increased C-reactive protein, whether or not confirmed by a positive blood culture, according to the NICU protocol. Given that drawing blood from 1.9 F catheters is not feasible, we considered a catheter-associated bloodstream infection to be the presence of at least one positive peripheral blood culture with clinical signs of sepsis and isolation of the same germ in a semi-quantitative catheter-tip culture (> 15 CFU).[9] All catheters underwent semi-quantitative cultures upon removal.

Statistical methods

A Kaplan-Meier plot was used to analyze the events during the catheter's useful life. 'Survival' was defined as the maintenance of patency until elective withdrawal. The groups' survival curves were compared using a log rank test. The differences between the time of permanent and continued infusion, demographic data and other means were analyzed with the T test. The significance level for intergroup differences was $P < 0.05$. Tests and plots were performed using the SPPS® version 13.0 software (SPPC Inc, USA, 2004).

RESULTS

Table 1 summarizes the each group's characteristics. No significant intergroup differences were found regarding gender, birth weight, gestation age, and time of continued pump infusion, time of catheter permanence and time of parenteral nutrition therapy. No catheter was used as the exclusive access for PNT, and all were used for multiple infusions, with attention to the compatibility of drugs to ensure flushing with saline between infusions of incompatible drugs. One extremely low-birth weight preterm newborn suffered a pulmonary hemorrhage due to a thrombocytopenia for fungal sepsis (*Candida parapsilosis)* and was excluded from Group 1 due to contraindication for heparin. We analyzed 133 newborns, with one catheter each; 64 in Group 1 (heparin) and 69 in Group 2 (saline).

No significant difference was found for the number of de novo occlusions between the groups (26 for Group 1, or 31/1,000 catheter-days; 36 for Group 2, or 36/1,000 catheter-days; $P = 0.2$; Figure 2). In Group 1, 5 catheters had 9 relapsed obstructions following very successful clearance attempts. In Group 2, 19 catheters had 40 relapses ($P < 0.0001$), showing the protective role of heparin against obstruction relapses (Relative Risk = 0.36). However, heparin failed to prevent withdrawals due to permanent obstructions (3 catheters in Group 1 and 8 in Group 2; $p = 0.24$). A spontaneous rupture was detected for 1 catheter in Group 2, resulting in removal of the catheter. Of the permanent occlusions, 2 catheters were ruptured during clearance attempts in Group 1 and 2 in Group 2. The ruptures were in the soft silicone portion, away from the insertion. A total of 35 clearance attempts were performed for Group 1, which were successful in 32 episodes (91.4%); for Group 2 there were 74 attempts, which were successful in 68 episodes (89.4%).

Table 1 – Group characteristics

	Group 1 (heparin)	Group 2 (saline solution)	p value
Number of patients	64	69	
Gestation age (weeks)	33.3 (25.4 – 39)	32.3 (24.8 – 41)	0.403
Weight (Kg)	1.64 (0.66 – 4.05)	1.58 (0.63 – 4.81)	0.521
Age by insertion (days)	3.63 ± 15.7	3.57 ± 18.7	0.123
Male	32 (50)	36 (52.2)	0.901
Time of infusion with infusion pump (days)	12.4 ± 10.7	11.7 ± 9.5	0.712
Patients with NPT	26 (40.6)	29 (42)	-
Time with NPT (days)	12.3 ± 10.5	18.2 ± 22.9	0.230
Permanence of the catheter (days)	13.2 ± 10.0	14.2 ± 9.6	0.611

NPT – parenteral nutrition therapy. Results expressed as n (%), mean ± standard deviation or median (minimum-maximum).

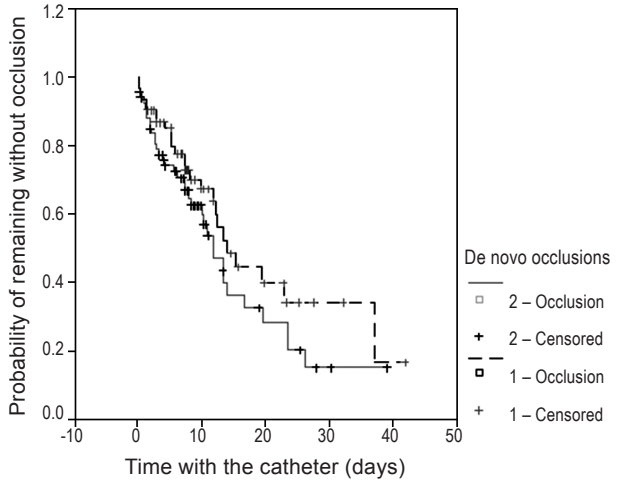

Figure 1 – Kaplan-Meier plot showing the probability of de novo occlusions for both groups during the time of the catheter permanence (P = 0.203).

For catheter tip cultures, in group 1 coagulase-negative staphylococci were isolated in 3 cases, while for group 2 coagulase-negative staphylococci were found in 1 patient and *Klebsiella pneumonia* in 1 patient. This case [*Klebsiella*] was the only one with a confirmed catheter-associated bloodstream infection that identified the same agent with the same sensitivity profile in a peripheral blood culture. This catheter was removed due to infection; catheters with no definite occlusion were electively removed.

Grade I or II intracranial hemorrhages were found in 5 patients in Group 1 and 10 patients in Group 2 (P = 0.12). A Grade III hemorrhage was seen in 1 patient in each group (P = 0.97). Overall, 40 ultrasound tests were performed in Group 1 newborns and 38 in Group 2. Thrombocytopenia during the hospital stay was seen in 12 Group 1 newborns, one of which was congenital, while the other 11 were associated with bacterial sepsis. For Group 2, 18 cases of thrombocytopenia were seen, in one case associated with a hypertensive disease during pregnancy and the remaining 17 with either fungal or bacterial sepsis. No statistically significant intergroup difference was seen for thrombocytopenia (P = 0.16).

DISCUSSION

Several approaches have been used to maintain catheter patency in newborns, including keeping a minimal infusion flow rate, changing the tubes frequently, and avoiding the infusion of blood and blood components. The most common intervention found in the literature is heparin continued infusion in parallel to or in combination with PNT. In the article by Shah et al., continued heparin at 0.5 U/Kg/hour in combination with PNT was evaluated for the maintenance of PICC patency in a randomized blinded trial conducted in a NICU. The incidence of occlusion was lower in the group receiving heparin as compared with the group receiving PNT alone, reducing the risk of occlusion by 47%.[6] In a previous meta analysis, Shah and Shah failed to find conclusive evidence of the benefit of heparin use: 2 trials reported a benefit, 1 reported harm and 2 reported no difference.[10] A study by Kamala et al. showed a reduced number of obstructions in the catheters with heparin use, however, the difference was not statistically significant, likely due to inappropriate sample characteristics.[11] In spite of the paucity of evidence, 'maintaining the line with heparin' has been a common practice worldwide for almost 30 years.[4,5]

If studies of continued heparin use are rare, intermittent heparin trials for any type of central catheter are even rarer. Smith et al. reported that intermittent heparin flushes (heparin 10 U/mL, 5 mL twice daily) in 14 oncologic pediatric patients with semi-implanted central catheters resulted in no benefit; however, no conclusion can be drawn from such a small sample.[12] Another meta analysis that evaluated the effectiveness of heparin flushes or continued heparin for peripheral venous access patency also found no benefit.[4] The 2 described meta analyses were impacted by the studies heterogeneity, with largely variable heparin doses and very different dosage schedules. In another trial, Schilling et al. compared heparin to saline flushes in 360 children with 599 central catheters; this trial included several types of catheters and a largely heterogeneous sample of patients. No occlusion rate differences were found in that trial.[2]

In our trial, a low-dose of heparin for intermittent flushes was not shown to be better than saline solution for preventing de novo obstructions. However, after successful clearance following the first obstruction episode, the maintenance of patency using saline was troublesome because there were more obstruction relapses than when using heparin flushes. In other words, in the no-heparin group, after the first obstruction episode the catheters tended to remain dysfunctional, requiring more frequent clearance attempts.

Clearance attempts entail risks of rupture, even when thrombolytic drugs are used, because the solution is infused into an obstructed catheter. The clearance technique used in this study was originally developed for use with thrombolytic agents, sucked into the catheter

lumen by the negative pressure of the syringe,[7] and was chosen because of the evident mechanical effects that may help to clear the obstruction. Ruptures can occur when flushing of the catheter (positive pressure) against resistance is attempted. The catheters (BD First PICC®) we used have a soft silicone extension that connects the catheter to the hub. This is the most mechanically vulnerable part, and it commonly inflates like a balloon when an infusion against resistance is attempted; ruptures occurred at this location. As the ruptures were not close to the insertion site and were incomplete, there was no risk of embolism. The risk of rupture during clearance maneuvers should be considered and weighed against the risks of insertion of a new central venous line.

Heparin doses in this study could be considered a minimal risk, given that 0.5 mL of a 10 U/mL heparin solution provides a dose of 5 units every 4 hours, for a total of 30 U/daily. Heparinization doses, i.e., those sufficient to cause significant coagulation changes, are from 50 to 100 U/kg every 4 hours.[8] Therefore, coagulation disorders or worsening of active bleedings are not anticipated with this dosage schedule. No other adverse events that could be ascribed to heparin occurred.

The limitations of this study include its open-label (non-blinded) nature and the lack of a no-flushing control group that was maintained with continued infusion only. The high rate of observed obstructions challenges the effectiveness of this method. Because the newborns' mean weight was 1.5 kg, these data cannot be extrapolated to newborns who weigh less than 1 kg because of a higher risk of bleeding and infection.

CONCLUSION

Intermittent heparin flushes of newborns' PICCs are beneficial only for reducing obstruction relapses after successful clearance maneuvers. Heparin failed to prevent de novo obstructions or withdrawal due to permanent obstruction.

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RESUMO

Objetivo: Verificar se a heparina em lavagens intermitentes é eficaz em reduzir oclusões de cateteres centrais inseridos perifericamente em recém-nascidos.

Métodos: Estudo randomizado, aberto, controlado, prospectivo. Os recém-nascidos foram alocados em dois grupos para receber lavagens ("flushes") com 0,5 mL da solução de heparina 10UI/mL (Grupo 1, n = 64) ou com 0,5 mL de salina (Grupo 2, n = 69), a cada 4 horas através do cateter central inserido perifericamente. Foram realizadas manobras de desobstrução por pressão negativa ("3-way stopcock method") nos casos de oclusão.

Resultados: Foram incluídos 133 recém-nascidos. Não houve diferença significativa no número de oclusões inéditas entre os grupos (26 no grupo 1, ou 31/1000 dias de cateter; 36 no grupo 2, ou 36/1000 dias de cateter, P = 0,19). No grupo 1, 5 cateteres apresentaram 9 recidivas da obstrução, após uma tentativa de desobstrução bem sucedida. No grupo 2, 19 cateteres apresentaram 40 recidivas (P <0,0001), mostrando papel protetor da heparina contra recidivas da obstrução (risco relativo = 0,36). Contudo, a heparina não evitou a retirada por oclusão definitiva (3 cateteres no grupo 1 e 8 no grupo 2, P = 0,24).

Conclusão: A heparina intermitente não é eficaz em evitar oclusão dos cateteres centrais inseridos perifericamente neonatais. Apenas reduz as recidivas, se realizadas manobras de desobstrução.

Descritores: Heparina; Recém-nascido; Cuidados críticos; Cuidados de enfermagem; Cateteres de demora

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