A randomized trial of heparin and saline for maintaining intravenous locks in neonates

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A Randomized Trial of Heparin and Saline for Maintaining Intravenous Locks in Neonates

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PURPOSE. To determine the effects of saline, heparin 2 units (U) per ml saline, and heparin 10 U/ml saline flush solutions on the duration of intravenous (IV) locks and the incidence of IV infiltration in neonates.

DESIGN. Randomized double-blind experiment.

SETTING. Tertiary-care nursery.

PARTICIPANTS. Neonates (N = 90) hospitalized at birth in the intensive, intermediate care, or newborn units.

MAIN OUTCOME MEASURES. Total hours from the time the IV was inserted to the time the IV was removed; hours from the time the IV was first flushed to the time the IV was removed; number of IVs removed because of infiltration.

RESULTS. No statistical or clinical differences between the three groups for duration of IV nor for incidence of complications.

CONCLUSIONS. The use of heparin in IV lock flush solution did not affect the duration of IV locks nor the incidence of infiltration in neonates.

Key words: Heparin, neonate, peripheral catheterization

It has been well-established in the adult population that saline is as efficacious as a heparin solution in maintaining patency of intravenous (IV) locks (Epperson, 1984; Goode et al., 1991; Smith et al., 1990; Tuten & Gueldner, 1991). Several studies have been done in the pediatric population (Kleiber, Hanrahan, Fagan, & Zittergruen, 1993; Lombardi, Gunderson, Zammett, Walter, & Morris, 1988) showing that saline and heparin are comparable for maintaining IV locks in children.

The results of previous studies done with pediatric and adult subjects should not be generalized to neonates for several reasons. First, neonates metabolize heparin differently from adults (McDonald, Jacobson, Hay, & Hathaway, 1981) and have a wider range of response to heparin (D’Errico, Shayevitz, & Martindale, 1996). Second, heparin intake among very-low-birthweight (VLBW) babies has been associated with intraventricular hemorrhage (Malloy & Cutter, 1995). For these reasons the use and dosage of heparin with neonates must be carefully controlled. The third difference between the neonatal population and older children and adults is that VLBW infants require very small IV catheters (24–26 gauge). The small-sized lumen may contribute to clot formation within the catheter. Additionally, the tiny vessels in which IVs are placed in VLBW babies may adversely affect the duration of patency. Another difference between neonates and adults is that IV sites are not routinely changed every 72 hours in the neonatal patient. Sick infants often require months of IV therapy, and veins become scarce. IV sites usually are used as long as the IV is patent and without signs of infection or infiltration.

The purpose of this study was to determine the efficacy of three different IV flush solutions in maintaining
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the patency of IV locks in neonates. The test solutions were: plain normal saline, saline with heparin 2 U/ml (low-dose heparin), and saline with heparin 10 U/ml (high-dose heparin). The addition of the low-dose heparin arm of the study was suggested by the physicians in the NICU. They were interested in decreasing patients’ exposure to heparin and thought that a small amount of heparin might be as effective as the heparin 10 U/ml flush that was used routinely in the study units. The null hypotheses were:

1. There are no significant group differences between the duration of IV locks flushed with saline, low-dose heparin, or high-dose heparin; and

2. There are no significant group differences for the incidence of IV lock infiltration (erythema, induration, leaking at the IV site, resistance to flushing) in IVs flushed with saline, low-dose, or high-dose heparin.

Literature Review

Few researchers have focused on the neonatal population when investigating the effects of flush solutions on IV duration. Danek and Norris (1992) used a randomized sequential double-blind design to study the effects of normal saline versus dilute heparin in infants and children with 22-gauge \((n = 40)\) and 24-gauge \((n = 120)\) catheters. During a 1-month period, all children and infants with IV locks inserted for the administration of medications, colloids, and parenteral lipids were entered into the study. The patients were in the general pediatric, pediatric intensive care, neonatal intensive care, and newborn nursery units. Following routine hospital procedure for the flushing of IV locks, nurses flushed each IV lock with either a 1-ml heparin solution \((10 \text{ U}/\text{ml})\) or 1 ml normal saline. Locks were flushed following each catheter use or every 8 hours. Sixty-nine percent of the study population was younger than 1 year of age, and 75% of the catheters examined in the study were the smallest size, 24 gauge. The investigators found no significant difference in catheter longevity for 22-gauge catheters flushed with normal saline or heparin solution; however, 24-gauge catheters flushed with the heparin solution had a significantly longer life span than those flushed with normal saline. The authors recommended further study for small-gauge catheters before changes in flushing procedures are made.

Kotter (1996) studied 118 24-gauge catheters that were used exclusively for intermittent infusions in neonates and found no difference in mean hours of duration between IV locks flushed with normal saline (36 hours) or 10 units heparin per ml of saline (34.5 hours). The groups were comparable for the types of medications given through the IVs and for the reasons for discontinuation. The author sites the frequency of flushing — every 4 hours — as a possible reason for the discrepancy between her findings and those of Danek and Norris (1992).

In a study of 463 children up to age 13, Beecroft and colleagues (1997) report that IVs flushed with a 10-U heparin solution were patent for a mean of 35 hours compared with 30.6 hours for those flushed with saline. In further analysis, the authors report that IVs flushed with heparin solution were patent longer in the group of children under 2 years of age.

A brief report by Goldberg, Givelichian, and Sankaran (1997) describes a double-blind randomized trial of saline versus 4-U heparin solution for 47 neonates with 24-gauge IV catheters. The IVs flushed with the saline solution lasted significantly longer than those in the heparin group.

Others have investigated the efficacy of heparin in continuous peripheral venous infusion in neonates. Treas and Latinis-Bridges (1992) studied a convenience sample of neonates in a Level III NICU. The control group consisted of 49 neonates with 122 peripheral IV catheters to which no heparin was added to their IV infusate or irrigating solution. The experimental group consisted of 63 neonates with 132 IV catheters, to which one half unit of heparin per ml of IV infusate and irrigating solution was added. The location of the IV catheter was comparable between the two groups. Infiltration was the most common reason for removing the catheter for both groups. The no-heparin group received significantly more medi-
cation than the heparin group, while the heparin group received more parenteral nutrition, lipids, calcium, and higher concentrations of glucose. The mean duration of IV for the heparin group (62.75 hours) was significantly longer than the mean duration of IV for the no-heparin group (27.3 hours). The Cox proportional hazards model was used to determine whether the covariates (lipids, total parenteral nutrition, calcium, blood transfusion, glucose concentration, medication infused through the line) affected duration. The heparin additive was the only covariate that influenced catheter patency significantly. Wright, Hecker, and McDonald (1995) also found that the addition of just one unit of heparin per ml of continuous infusate lengthened the duration of IVs in children.

The published research on this topic is not sufficient to guide clinical practice. Questions remain regarding the usefulness of heparin in extending the duration of IV locks in neonates and dosage at which heparin might be effective. The current research study was undertaken to investigate this question.

**Methods**

**Sample**

Subjects were neonates (N = 90) requiring peripheral intermittent IVs who were hospitalized in the newborn, intermediate care, or intensive care nurseries at a large midwestern teaching hospital. Exclusion criteria included babies who had received any anticoagulant medication within the previous 48 hours, who weighed less than 800 g, or whose parents were not conversant in English. The study was approved by the institutional review board, and written informed consent was obtained from the parents.

**Procedure**

An experimental, randomized, double-blind design was used. Patients were entered into the study using a previously established random allocation list when an order was written to “lock” a peripheral IV. The subjects were assigned to have IV locks flushed with one of three solutions: (1) preservative-free normal saline; (2) preservative-free normal saline with heparin 2 U/ml (low-dose heparin group); or (3) preservative-free normal saline with heparin 10 U/ml (high-dose heparin group). Pharmaceutical Services, a division of the College of Pharmacy at the hospital, produced batches of the three types of treatment solutions in identical syringes, which were coded. Only the primary investigator had access to the randomization list and to the code. Lists with the subject and code numbers were hung in each of the nurseries (NICU, intermediate care, and normal newborn). When an infant was entered into the study, the next available number was assigned. For the life of the IV site, the IV was flushed only with the assigned solution. Only one IV site per subject was allowed. All IV locks were flushed at least every 6 hours.

Daily rounds were made by a member of the research team to collect data. Specific information collected from the hospital record included the patient’s age, diagnosis, time and date of IV insertion and discontinuation, catheter type, IV location, type of medications given through the IV, number of flushes given, reason for IV removal, and incidence of complications.

Checking the IV site for complications and documenting the assessment are routinely done in the nurseries every 6 hours and with every medication administration. Prior to initiation of the study, the nurses who were assigned to the units involved received education on the standardized method for locking IVs, identifying IV complications, and criteria for discontinuing IV catheters. Complications of IV therapy indicative of infiltration were defined as resistance with flush, erythema, induration, or leaking at the IV site.

Data were collected for 11 months. Total duration of IV life was defined as the number of hours from the time the IV was inserted to the time it was discontinued. It was common for neonates to have fluids infusing continuously through the IV before the IV was locked. For example, a neonate may have an IV in place and be receiving fluids and/or antibiotics until full enteral feedings could be achieved. Then the IV would be locked for intermittent
antibiotic therapy. Therefore, the time from the first IV lock flush to the time of IV discontinuation also was measured.

The number of subjects who received potentially irritating IV medications was tracked for group comparisons. Medications chosen for tracking were based on a review of the literature and those commonly used with sick neonates. They included nafcillin, aminoglycosides, phenytoin, parenteral nutrition, lipids, calcium, and packed red blood cells. Analysis of variance (ANOVA) was used for analyzing interval data and chi-square was used for categorical data. Alpha was set at 0.05.

Results

The final sample consisted of 90 IV sites in 90 subjects: 27 in the normal saline group, 28 in the heparin 2 U/ml group, and 35 in the heparin 10 U/ml group. The groups were comparable for birth weight ($F_{2,87} = 1.139, p = .325$), gestational age ($F_{2,87} = 1.089, p = .341$), IV location ($\chi^2 = 6.766, p = .3429$), and reason for IV discontinuation ($\chi^2 = 1.599, p = .808$), as described in Table 1. Seventy-five of the 90 infants studied (83%) received potentially irritating medications through the IVs. Of those infants not receiving medications or blood through the IV, 4 were in the saline group, 7 received low-dose heparin flushes, and 4 were in the high-dose heparin group.

There were no statistically significant group differences for duration of the IV catheter as measured by the total number of hours from the time the IV was inserted to the time it was discontinued ($F_{2,87} = 0.13, p = .878$) or number of hours from the time of the first IV lock flush to the time the IV was discontinued ($F_{2,87} = 0.13, p = .879$). The means and standard deviations (SD) for each group are in Table 2.

Because the ANOVA test does not provide information on the direction of variation among groups, survival analysis was conducted comparing the duration of IVs in the saline group with the duration of IVs in the heparin 10 U/ml group. Survival functions add precision to statistical analyses because the “time to event” factor is taken into consideration. In this case, the time from IV insertion to discontinuation was compared. The survival curves are shown in Figure 1. The Wilcoxon (Gehan) statistic for the curve

<table>
<thead>
<tr>
<th>Table 1. Group Comparisons</th>
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<tr>
<td><strong>Factor</strong></td>
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<td>Birthweight range (grams)</td>
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<td>Mean</td>
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<tr>
<td>SD</td>
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<td>IV location</td>
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<td>Hand</td>
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<tr>
<td>Arm</td>
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<tr>
<td>Reason for discontinuation</td>
</tr>
<tr>
<td>Infiltrated</td>
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<tr>
<td>No longer needed</td>
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<tr>
<td>Accidental</td>
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<tr>
<td>Missing data</td>
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</tbody>
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All group comparisons nonsignificant (p>0.05)
Table 2. Duration of IV: Group Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Heparin 2 U/ml Saline</th>
<th>Heparin 10 U/ml Saline</th>
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<tr>
<td></td>
<td>(n = 27)</td>
<td>(n = 28)</td>
<td>(n = 35)</td>
</tr>
<tr>
<td>Hours from insertion to discontinuation Mean 67.09 SD 33.08</td>
<td>63.84</td>
<td>33.08</td>
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<tr>
<td>Hours from first flush to discontinuation Mean 38.08 SD 29.43</td>
<td>40.43</td>
<td>24.11</td>
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</table>

All group comparisons nonsignificant (p>0.05)

Discussion

In this randomized double-blind experiment there were no statistically significant differences in duration of IV locks flushed with normal saline, heparin 2 U/ml saline, or heparin 10 U/ml saline. This study differs from the Danek and Norris (1992) and Kotter (1996) studies in that many of the infants had continuous IV fluids running through the IVs prior to locking them for intermittent use. There are very few neonates in our units who have IVs inserted for intermittent use only. An additional point to keep in mind is that none of the continuous infusate contained heparin. The only heparin given to the study infants was the heparin in the flush solutions.

The protocol used in our nurseries for flushing intermittent IVs may have contributed to the differences between our findings and those of Beecroft et al. (1997) and Danek and Norris (1992). In our units, the nurses

Figure 1. Survival Guide

Wilcoxon (Gehan) statistic .016 (p = .89)
flush IVs before every medication in order to check for patency, or every 6 hours, whichever comes first. They use a positive-pressure technique, clamping the tubing while the last 0.1 cc of flush is being infused. The rationale behind clamping while exerting positive pressure is that it may prevent a backflash of blood cells into the catheter lumen (Shearer, 1987). There have been no systematic investigations of this technique, however.

As with all clinical studies using very small sample sizes, the results must be interpreted with caution. The statistical power in this study was low. That means there is large chance of making a Type II error, accepting the null hypothesis when there really is a difference between population groups. In order to detect a clinically significant difference (specified to be 12 hours) between saline flushed and heparin groups and to achieve a power of .8, we calculated that a sample size of 130 per group was needed. Limitations in funding and investigator time did not allow for such a large sample.

Conclusions

The use of heparin in IV lock flush solutions continues to be an issue for neonatal nurses. In this study, there was no statistically significant difference between IVs flushed with heparin solution or those flushed with normal saline with regard to either duration of the IF locks or incidence of infiltration. The cost of the heparin solution and the stinging pain that accompanies the injection could be avoided if saline were shown to be an acceptable flush solution. Students and researchers who have conducted small-scale studies such as this one are encouraged to publish their findings. A meta-analysis of small studies might provide the answer to this lingering question.

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