Comparison of Normal Saline and Heparinized Saline for Patency of IV Locks in Neonates

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In this randomized double-blind experiment of 49 neonatal intensive care unit patients, probable time to catheter failure was significantly longer \( (p = .0358) \) for catheters flushed with heparinized saline \( (\text{median} = 127) \) compared with those flushed with normal saline \( (\text{median} = 39) \). This is in contrast to the nonsignificant difference \( (p = .841) \) in mean scores for six heparin-flushed catheters \( (M = 41.5 \text{ hours}, SD = 44.0) \) compared with 18 saline-flushed catheters \( (M = 30.4 \text{ hours}, SD = 20.8) \) discontinued for reasons other than completion of treatment. We concluded that survival time analysis is necessary when evaluating results of time-dependent studies in which the end point may not be elective.

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THE USE OF NORMAL saline as the flush solution to maintain patency in large-gauge intravenous (IV) catheters \( (16 \text{ to } 22 \text{ G}) \) in the adult population has become an acceptable standard of practice in acute care and home care across the country. The use of heparinized saline flush solution is the more common protocol in the pediatric population and, more specifically, the neonatal population; however, there is no national standard (Bosser & Beecroft, 1994). Our search to identify a national standard yielded a variety of protocols in current use across the country.

Insertion of peripheral catheters in neonates can be difficult, painful, and time consuming. Reducing the number of IV punctures by capping IV accesses is one way of decreasing these painful procedures. The current practice in our neonatal intensive care unit (NICU) to maintain the patency of capped IV accesses is to flush IV locks with normal saline before and after administration of a medication, then flush again with heparinized saline to avoid an interaction of these drugs with heparin. This additional heparin carries the potential risk for intraventricular hemorrhage and other coagulopathies (Malloy & Cutter, 1995; Spadone et al., 1992). It is posited that if flushing with normal saline is as effective as flushing with heparinized saline, there will be financial savings to patients and institutions, in addition to reducing the clinical risks of heparin (Goode et al., 1991). The current costs of using heparinized saline include a pharmacist’s time to prepare the solution and additional costs of materials used in the preparation. Nursing time is increased based on the multiple flushes within standard protocols. In summary, the benefits of not using heparin include: (1) decreased risk for incompatibility with other medications, (2) possible decreased risk for intraventricular hemorrhage and other coagulopathies, and (3) savings in both cost and time. These benefits must be weighed against the risks for increased failure of peripheral IVs and subsequent repeated painful procedures.

REVIEW OF THE LITERATURE

Since the mid-1980s, interest in studying the safety, tolerability, and effectiveness of normal saline flushing of peripheral IV catheters in children has increased. Findings have been inconsistent for the primary variable of interest, duration of patency. Several studies included children ranging in age from 1 to 18 years (Beecroft et al., 1997; Danek & Norris, 1992; Kleiber, Hanrathan, Fagan, & Zittergruen, 1993; Lombardi, Gundersen, Zanetti, Walters, & Morris, 1988; McMullen, Fioravanti, Pollack, Rideout, & Sciara, 1993; Mudge, Forcier, & Slattery, 1998); one study did not report the age range of the sample (Hanrathan, Kleiber, & Fagan, 1994). As might be anticipated, this wide
age variation in the studies precluded control over the size of the IV catheter. Catheter size was cited as predictive of longevity, with larger catheters remaining patent longer than smaller catheters (Beecroft et al., 1997; Danek & Noris, 1992; Mudge et al., 1998; Paisley, Stamper, Brown, Brown, & Ganong, 1997).

The use of survival statistics to analyze the duration of patency was considered an important parameter for critique and synthesis. Comparison of findings across studies was confounded by the lack of clear criteria and definitions for discontinuing catheters. Generally, catheters in the studies were discontinued for "elective" reasons when the treatment was no longer needed and for "nonelective" reasons when there was infiltration, leakage, occlusion, phlebitis, or accidental dislocation. It was not always clear which catheters were included in the analyses. If the duration of patency was analyzed for all catheters regardless of the reason for discontinuation, the reported findings could erroneously lead the reader to false conclusions. For example, results of one study were reported as no statistically significant difference in hours of duration for 124 catheters based on saline or heparin flush solutions (Kleiber et al., 1993). The researchers further reported that there was not a statistically significant difference among elective and nonelective reasons for discontinuing catheters. However, only 20 catheters in the saline group and 14 catheters in the heparin group were removed for nonelective reasons. There was no reported analysis on length of patency for these 34 catheters. There may be a difference in survival probability based on those catheters that continued to be patent until discontinued for elective reasons.

In two of seven studies that included neonates, there was no statistically significant difference in duration of patency between two flushing methods based on life-table analyses (Hanrahan, Kleiber, & Berends, 2000; Paisley et al., 1997). When comparing the mean difference in duration of patency for 43 catheters flushed with heparinized saline and 75 catheters flushed with normal saline, Kotter (1996) found no statistically significant difference. All catheters were discontinued for nonelective reasons. The other studies were not clear in how they censored the discontinued IV catheters for survival analysis (Heilskov, Kleiber, Johnson, & Miller, 1998; Nelson & Graves, 1998), or they did not use survival analysis to determine duration of patency differences (Golberg, Sankaran, Givelichian, & Sankaran, 1999). The sample size for catheters discontinued for nonelective reasons in these latter studies did not meet the predetermined optimal sample size based on power analysis for comparative statistics. The potential for type II errors must be considered, i.e., the possibility that sample sizes were not adequate to detect a significant difference in mean duration of time, if it existed.

Type II errors are an important clinical consideration when synthesizing results regarding the use of heparinized or normal saline flushes in pediatric patients and, more specifically, critically ill neonates. One way of avoiding type II errors is to have an adequate sample size to detect differences when they are present. For example, McMullen et al. (1993) used power analysis to determine an optimal sample size of 146 based on a clinically relevant 8-hour difference in longevity. Their well-designed study reported on comparison of mean duration of patency, age, medication type infused, and catheter size and placement for 142 subjects. The researchers also reported the number of catheters that were discontinued nonelectively, i.e., catheters for which the heparin/saline comparison of duration is clinically and statistically meaningful. They reported a nonsignificant difference between the two groups in mean duration for catheters remaining patent longer than 48 hours; however, the sample size had been reduced to 81 subjects. Accepting these findings as valid may support a type II error. This is particularly important when changing practice could increase the risk for catheter occlusion and the potential for repeated venipunctures and related sequelae. One study had an adequate sample size for catheters \( N = 254 \) discontinued for clinical reasons and used life-table analysis to compare longevity between the flushing methods (Treas & Latinis-Bridges, 1992). In this study, heparinized flushing resulted in significantly longer duration of patency in 24 G catheters in neonates. However, findings in this study are limited to 24 G catheters with continuous infusions.

The reported standard for frequency of flushing time in the studies varied from no reported standard (Mudge et al., 1998) to a minimum of every 4 hours (Kotter, 1996; Paisley et al., 1997). In addition to flushing protocols, catheters also were
flushed before and after the administration of medications. Crews, Gannn, Rice, & Kee (1991) suggested longer intervals between flushing procedures may increase longevity, but also reported that the intervention was difficult to control because of individual practices, even when it was the independent variable of interest. Crews and colleagues did not find that the number of medications affected catheter longevity.

Control of flushing technique and data collection methods were addressed in most of the studies vis-à-vis standardized education of staff (Beecroft et al., 1997; Danek & Noris, 1992; Kotter, 1996; McMullen et al., 1993). In one study, all data collectors completed an IV certification course (Golberg et al., 1999). Attention to competency regarding flushing technique was not addressed. The number of data collectors and variability in flushing technique were cited as confounding variables in several studies (Beecroft et al., 1997; Crews et al., 1991; Mudge et al., 1998; Paisley et al., 1997).

This research project was proposed to address several of the gaps found in previous studies. Its purpose is to compare the effectiveness of heparinized and normal saline flushes in maintaining the patency of 24 G intermittent peripheral IV catheters in neonates requiring intensive care. The hypothesis stated that there would be no significant difference in the duration of patency of a 24 G IV lock in a neonatal patient when flushed with 0.5 mL of heparinized saline (2 U/mL), our standard practice, compared with 0.5 mL of 0.9% normal saline.

METHODS

This study used a double-blind experimental design. The setting was a 24-bed NICU averaging 500 admissions per year. Sample size was based on a 12-hour difference in the longevity of the IV lock. Power analysis for a Student's t-test determined an optimal sample size of 292 would provide a power of .80 with a two-tailed alpha less than .05. Inclusion criteria were all neonates younger than 30 days with a new 24 G IV lock 3/4 inch in length. Exclusion criteria were neonates with central catheters, recent surgery, a diagnosis of disseminated intravascular coagulopathy or idiopathic thrombocytopenia, or current or previous treatment of a patent ductus arteriosus with indomethacin. The study received approval from the hospital’s institutional review board.

Education of Staff

All nursing staff received in-service information regarding the study by the primary investigators. Nurses were instructed on study design and purpose and how to obtain informed consent, use the study protocol, determine IV lock patency, and complete the data collection tool. Competency was established for the flushing procedure by having each nurse pass a quiz on IV lock flush protocol with a score of 90% or higher and show proper IV lock flush technique. All staff nurses completed the requirements to participate in the study.

Procedure

After a physician order for an IV lock, three staff nurses, in addition to the study investigators, obtained informed consent from the parent(s). Only the first IV lock per infant was included in the study. When the first IV lock was discontinued for any reason, the infant was not re-enrolled for any subsequent IV locks. A color-coded label was placed on the islettes of infants enrolled onto the study.

Randomization of subjects occurred in the pharmacy on receipt of an order for study solution and a copy of the informed consent. The subject was randomized to receive either 0.5 mL of heparinized saline (2 U/mL) or 0.5 mL of 0.9% normal saline as the flushing solution. Study solutions were prepared, coded, and labeled in the pharmacy and delivered to the NICU. All staff, including the study investigators, were blinded to the study group. Only the pharmacist knew the results of the randomization.

All IV locks were flushed with the study solution every 3 hours according to protocol. Patency of the IV lock was assessed with each flush.

An IV lock was discontinued for the following noneffective reasons: (1) inability to flush the IV lock with 0.5 mL of solution within 10 seconds, (2) leaking around the insertion site or the connectors, (3) redness at the insertion site, (4) swelling greater than 1 cm in height at the insertion site, or (5) symptoms of pain shown by crying, grimacing, or withdrawal of the limb of the IV site.
Data Collection

Data were collected at the bedside by the nurses and recorded on a data collection tool developed by the investigators. The reason for discontinuing the IV lock was documented. When the IV lock was discontinued, the data collection tool was placed in a locked box that was accessed only by the investigators.

RESULTS

After 12 months of data collection, 49 infants (17 boys, 32 girls) were recruited onto the study. Twenty infants were randomized to the heparin group (control), and 29 infants, to the saline group (experimental). Gestational age for the sample ranged from 26 to 42 weeks, with a mean of 33.5 weeks ($SD = 3.8$). Chronological age ranged from 1 to 30 days, with a mean of 6.8 days ($SD = 6.9$). Mean birth weight was 2.11 kg ($SD = 0.875$), with a range from 0.52 to 3.89 kg. There were no statistically significant differences in sex determined by chi-square analysis. There were no statistically significant differences in birth weight, gestational age, or chronological age of subjects between the two groups based on Student’s t-test (Table 1).

The mean duration of patency for angiocatheters flushed with heparinized solution was 38.5 hours ($SD = 33.3$) compared with 34.4 hours ($SD = 27.3$) for angiocatheters flushed with normal saline. The difference was not statistically significant ($t = .457$, $df = 45$, $p = .650$). Catheters were discontinued for a variety of reasons; 21 catheters were discontinued based on completion of treatment (Table 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Sample ($N = 49$)</th>
<th>Experimental Group ($n = 29$)</th>
<th>Control Group ($n = 29$)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>17</td>
<td>8</td>
<td>9</td>
<td>.208</td>
</tr>
<tr>
<td>Girls</td>
<td>32</td>
<td>21</td>
<td>11</td>
<td></td>
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<tr>
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<td>$M = 2.17$</td>
<td>$M = 2.02$</td>
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<tr>
<td></td>
<td>$SD = .875$</td>
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<td>$SD = .83$</td>
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<td>$SD = 3.88$</td>
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<td>Chronological age</td>
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<td>$M = 5.65$</td>
<td>$M = 8.45$</td>
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<tr>
<td></td>
<td>$SD = 6.87$</td>
<td>$SD = 5.01$</td>
<td>$SD = 8.80$</td>
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</table>

*Significance based on unequal variances.

<table>
<thead>
<tr>
<th>Reason for Discontinuation</th>
<th>Heparinized Saline</th>
<th>Normal Saline</th>
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</thead>
<tbody>
<tr>
<td>Will not flush</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Leaking</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Discomfort/crying</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Redness</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Edema</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Treatment complete</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Multiple reasons could be checked.

Thirteen infants (27%) were administered ampicillin, cephalosporin, gentamycin, or vancomycin, alone or in combination, during the study period. There were no statistically significant differences in the number of the infants per group administered antibiotic therapy or in the mean number of antibiotic doses administered per group. Differences remained insignificant when catheters discontinued for nonselective reasons, i.e., leaking at the site, redness, edema, discomfort, or inability to flush, were examined.

For angiocatheters that were discontinued for a reason other than completion of treatment, the mean duration for heparin-flushed catheters ($n = 6$) was 41.5 hours ($SD = 44.0$) compared with 30.4 hours ($SD = 20.8$) for saline-flushed catheters ($n = 18$). Levine’s test for equality of variance showed a nonsignificant difference ($F = 2.77$, $p = .110$); therefore, Student’s t-test was used to compare the means. The difference in duration of patency was not statistically significant ($t = .850$, $df = 22$, $p = .404$). Because group sizes were very unequal, the nonparametric Mann-Whitney U also was calculated. Results were nonsignificant ($U = 51.00$, $p = .841$). There were no statistically significant differences in weight, days of life, or gestational age between subjects in the two groups.

Twelve of 18 catheters in the heparinized-solution group and 9 of 27 catheters in the saline-solution group were electively discontinued because IV therapy was completed. Kaplan-Meier survival analysis was used to estimate the probable time to failure for those catheters that were discontinued because of end of treatment (censored). Median survival distributions were significantly different ($p = .0358$), with longer time to failure in the heparin group (Figure 1). Estimated median survival time for the 12 censored catheters flushed
with heparinized solution (those discontinued when treatment was finished) was 127 hours compared with an estimated median survival time of 39 hours for the 9 censored catheters flushed with saline.

**DISCUSSION**

Like several of the previously reviewed studies, data collection was discontinued with a much smaller sample size than determined a priori for comparative statistical power, suggesting a potential type II error. Statistical power for comparing the duration of patency for catheters discontinued for nonelective reasons, calculated by Student’s t-test, was .09. With these findings, a sample size of 304 would be necessary to compare the hypothesized results, i.e., a 12-hour difference in mean hours of duration of patency for catheters discontinued for nonelective reasons.

The findings further support the need to use life-table analysis in studies examining the duration of time to survival. Even with this small sample size and the small amount of heparin used for the flush solution (2 U/mL), the estimated survival time for catheters flushed with heparinized saline was significantly longer than for catheters flushed with normal saline. This finding did not support our hypothesis, but supports previous findings in a study of neonates with continuous infusions and other studies of older children (Beecroft et al., 1997; Danek & Noris, 1992; Mudge et al., 1998; Treas & Latinis-Bridges, 1992).

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*The estimated survival time for catheters flushed with heparinized saline was significantly longer than for catheters flushed with normal saline.*

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A potentially confounding factor in the longevity of patency is adherence to the unit standard of flushing catheters every 3 hours. Documentation of the standard at this institution does not facilitate
statistical examination of the exact number of times per day each catheter was actually flushed. Adherence to the flushing procedure is assumed unless there is an exception to the standard of care and the reason for that exception is documented. This is current practice in most institutions today. Finding no difference in the number of antibiotic doses per group and the administration of very few other medications through the peripheral catheters can only serve as a proxy for this variable.

The reasons for discontinuing IV locks also were instructive. Multiple reasons could be indicated for the discontinuation of a catheter. Although it is important to point out that there were 29 catheters in the saline-flushed group and only 20 catheters in the heparinized-saline group, reasons for discontinuation of catheters suggest more problems with saline-flushed catheters. For example, more than three times the number of catheters in the saline-flush group were discontinued for “will not flush” than in the heparinized-saline group. A clear definition for determining catheter patency as used in this study should be carefully considered and documented in future studies.

Reasons for discontinuation of catheters suggest more problems with saline-flushed catheters.

CONCLUSIONS AND RECOMMENDATIONS

This study further supports the use of survival statistics as the appropriate method of analysis. Results of the survival probability analysis, even with this small sample, were statistically significant, with longer probability of survival in those catheters flushed with heparinized saline. Although small, the study provides further evidence for continuing use of heparinized saline as the standard flushing solution in infants with 24 G catheters (Beecroft et al., 1997; Danek & Noris, 1992; Mudge et al., 1998).

The study provides further evidence for continuing use of heparinized saline as the standard flushing solution in infants with 24 G catheters.

Acknowledging the lack of current national standards and inconsistent research findings regarding the use of normal saline for maintaining the patency of IV locks in premature infants, we recommend that our study be replicated using a larger sample size. We continue to support the theoretical advantages of normal saline as the solution of choice based on the potential for fewer adverse effects and decreased cost of administration. However, the advantages of saline may not be beneficial if IV starts are required more frequently. At this point, there may be enough research to support a meta-analysis of the multiple experimental studies and thus provide clinical recommendations with adequate statistical power and data to establish research-based guidelines.

REFERENCES


