Purpose: The primary purpose of this study was to compare the efficacy of 1.4 percent sodium citrate with heparin, 4 U/ml, for maintaining radial artery catheter patency in patients in the medical ICU.

Patients and Methods: Patients in the medical ICU (n = 40) were randomized to either a 1.4 percent sodium citrate or heparin 4 U/ml arterial line flush solution in a double-blind, parallel fashion. The flush solutions were continuously infused at approximately 3 ml/h over a maximum of 96 h. Catheter survival rates were compared using Kaplan-Meier survival curves. The frequency of catheter malfunctions and corrective manipulations were recorded and compared. Coagulation status (APTT, PT) and ionized calcium values were monitored to evaluate the systemic effects of sodium citrate.

Invasive arterial cannulation for the purpose of continuous blood pressure monitoring has become a routine part of modern intensive care. Arterial catheters also provide a continuous access for blood sampling, thus decreasing patient discomfort from repeated venous or arterial punctures. Patency of the arterial catheters is generally maintained with a continuous flush solution containing heparin. This pressurized solution is commonly referred to as an "arterial line flush."

The addition of heparin to fluids constantly infused through the arterial catheter (usually as a 0.9 percent sodium chloride solution) is performed to maintain catheter patency, and presumably, to reduce thromboembolic complications. Although this practice was widely adopted many years ago, its efficacy has been demonstrated only recently.

We recently reported the findings of a study that evaluated the efficacy of flush solutions containing 0.9 percent sodium chloride with and without heparin in maintaining patency of peripheral arterial catheters. The study showed the functional life span of arterial catheters to be significantly longer and require less manipulation when flushed with a heparin-containing solution (4 U/ml) vs a sodium chloride solution alone.

The decision to include heparin as an anticoagulant in arterial line flushes is important when one considers the possible systemic effects of the drug. The ability of low doses of heparin to cause thrombocytopenia and alterations in coagulation status has been well documented.

The use of sodium citrate as an alternative anticoagulant for use in arterial catheter flush solutions has been described. However, efficacy or safety trials for this flush solution have not been reported previously (to our knowledge). The primary objective of this study was to compare the efficacy of a 1.4 percent sodium citrate solution with a heparin 4 U/ml solution in maintaining patency of peripheral arterial catheters. Safety was assessed by monitoring subjective effects and effects of the sodium citrate solution on systemic coagulation and serum ionized calcium.

Results: Ninety-four percent of catheters flushed with sodium citrate were functional at 48 h compared with 88 percent for heparin (p>0.05). At 96 h, 80 percent vs 88 percent of the catheters were functional in the citrate and heparin groups, respectively (p>0.05). Frequency of catheter malfunctions did not differ between the two groups. No systemic effects of sodium citrate were observed.

Conclusion: Arterial catheter flush solutions containing sodium citrate (1.4 percent) are an effective and safe alternative to heparin in patients requiring peripheral arterial catheterization.

**ANOVA** = analysis of variance; **APTT** = activated partial thromboplastin time; **PT** = prothrombin time

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**Arterial Catheter Patency in MICU (Branson et al)**
consent was obtained from each patient prior to entry into the study. Patients were screened for adequate collateral flow using a modified Allen's test. Patients selected for entry into the study must have had no coagulation disorder, as evidenced by the prothrombin time (PT) and activated partial thromboplastin time (APTT) being within 10 percent of control and a platelet count above 50,000/mm³. Patients could not be receiving systemic anticoagulation other than subcutaneous low-dose heparin therapy. The study was approved by the University of Kentucky Medical Institutional Review Board and written informed consent was obtained from each patient prior to entry into the study.

This was a double-blind study in which patients were randomly assigned to one of two groups. Patients in group 1 received arterial line flush solutions consisting of 1.4 percent sodium citrate (trisodium citrate, Cytosol Laboratories, Inc, Braintree, Mass) in 0.9 percent sodium chloride. Similarly, patients in group 2 received arterial line flush solutions containing heparin 4 U/ml in 0.9 percent sodium chloride. The arterial line consisted of a standard arterial flush system using an arterial pressure monitoring tubing (Cobe, Cobe Inc, Lakewood, Colo) and a pressure system device (Tyco, Tyco Laboratories, Inc, Exeter, NH). The flow rate for the flush solution was approximately 3 ml/h. The study period was a maximum of 96 h to coincide with the institution's policy on replacement of peripheral arterial catheters.

Patients could be reentered into the study one additional time if their catheter remained patent for the entire study period, if no ill effects from the flush occurred, and if another catheter was being placed. Patients reentered were also rerandomized for treatment. Catheter failure was defined as catheter discontinuation secondary to it becoming nonfunctional for reasons other than a personnel management error, 96-h maximum time limit for catheter placement, or the arterial line no longer being clinically necessary. Pressure wave dampening often precedes catheter occlusion; thus, the incidence and interventions required to correct the pressure wave dampening were closely monitored and recorded at the end of each 8-h shift. Frequency of pressure wave dampening, inability to withdraw blood freely, and corrective manipulations were recorded as occurring zero times, one to five times, six to ten times, or greater than ten times per 8-h shift.

The APTTs and PTs obtained from the catheter were compared with the same laboratory values obtained simultaneously by venipuncture. Changes in APTT, PT, and serum ionized calcium were compared with baseline and between-treatment groups.

The functional life span of the arterial catheters was evaluated using life-table analysis (Kaplan-Meier survival curve) and compared statistically using the Mantel-Haenszel test. Standard χ² analysis was used to test all nominal data. Analysis of variance (ANOVA) and the unpaired t test were employed to test differences in continuous data. The number of interventions required to correct pressure wave dampening and catheter occlusion were compared by assigning scores to the respective frequency intervals for catheter manipulation. The Mann-Whitney U test was used to test for statistical significance. All data are presented as mean ± SD.

RESULTS

For safety purposes, catheter patency results were analyzed after data collection on 10, 20, 30, and 40 catheters. The study continued until data were collected on 20 catheters in each group. A total of 35 patients were enrolled. Five patients were enrolled twice; three patients received both treatments, one received heparin twice, and one received citrate twice. Demographic and laboratory data are shown in Table 1. The citrate and heparin groups were well matched with respect to age and sex (p>0.05). Respiratory failure was the most common diagnosis in both groups (11 in heparin, 15 in citrate). The number of attempts to cannulate the radial artery was similar between the two groups (p>0.05). Platelet counts were similar between the two groups. Platelet counts ranged from 107,000 to 742,000/mm³ in the citrate group and from 127,000 to 543,000/mm³ in the heparin group.

The total number of 8-h shifts completed was 190 (mean = 9.05 ± 3.3) and 173 (mean = 9.10 ± 3.1) for the

Table 2—Catheter Malfunctions and Interventions by Treatment

<table>
<thead>
<tr>
<th>Event/Malfunction</th>
<th>Citrate</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dampened waveform</td>
<td>No. of patients</td>
<td>11</td>
</tr>
<tr>
<td>No. of shifts (%)</td>
<td>49 (25.8)</td>
<td>50 (28.9)</td>
</tr>
<tr>
<td>Catheter occlusion</td>
<td>No. of patients</td>
<td>6</td>
</tr>
<tr>
<td>No. of shifts (%)</td>
<td>14 (7.4)</td>
<td>11 (6.4)</td>
</tr>
<tr>
<td>Corrective manipulations</td>
<td>No. of patients</td>
<td>11</td>
</tr>
<tr>
<td>No. of shifts (%)</td>
<td>50 (26.3)</td>
<td>47 (27.3)</td>
</tr>
<tr>
<td>Frequency of manipulation</td>
<td>1-5</td>
<td>112</td>
</tr>
<tr>
<td>6-10</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>&gt;10</td>
<td>24</td>
<td>19</td>
</tr>
</tbody>
</table>

*Number of patients in which the event or intervention occurred.
†Number and percentage of 8-h shifts in which the event or intervention occurred.
citrate group and the heparin group, respectively. Catheter survival curves for the two treatments are shown in Figure 1. There were two catheter failures in the heparin group and three failures in the citrate group. At 48 h, 94 percent of the catheters flushed with sodium citrate solution were patent compared with 88 percent of the catheters flushed with heparin solution. The survival at 96 h was 80 percent and 88 percent for sodium citrate solution and heparin solution, respectively (p > 0.05). The frequency of occlusions and pressure wave dampening is given in Table 2 along with the frequency of manipulations made to correct malfunctioning catheters.

Serum ionized calcium levels at 0 and 72 h were not significantly different within or between treatment groups. Mean serum ionized calcium levels at 0 and 72 h were 2.35 ± 0.13 mEq/L and 2.31 ± 0.14 mEq/L for the sodium citrate group and 2.38 ± 0.27 mEq/L and 2.35 ± 0.23 mEq/L for the heparin group. Coagulation studies obtained simultaneously from the catheter and venipuncture at 0 and 24 h were highly correlated in both groups (heparin: PT r = 0.99; APTT, r = 0.98; and citrate: PT r = 0.95; APTT r = 0.87). Coagulation parameters collected at 24 h from the vein revealed no evidence of systemic anticoagulant effects from heparin or sodium citrate (Table 3).

**Discussion**

In a study of 35 patients in the general medical ICU with normal results of coagulation chemistry studies and normal platelet counts, we found no difference in patency between arterial catheters continuously flushed with a 1.4 percent sodium citrate solution vs a 4 U/ml heparin solution. Additionally, the number of occlusions and manipulations required to correct pressure wave dampening was similar between the two groups.

To our knowledge, this is the first reported prospective study investigating the use of 1.4 percent sodium citrate as a continuous flush solution for arterial catheters in adults. In a previous study from our institution, we demonstrated that 0.9 percent sodium chloride by itself works poorly in maintaining patency of arterial catheters. The addition of heparin to the flush solution resulted in an increased patency rate as opposed to the actual amount of citrate administered for regional anticoagulation during hemodialysis. These results suggested that constant, low-flow infusion of the flush solution is only in part responsible for maintaining patency of the catheter and that addition of an anticoagulant is also necessary.

Heparin has the potential to cause severe adverse effects, some of which appear to be independent of dose. In particular, heparin, even in low doses, has been associated with localized or disseminated thromboses, thrombocytopenia with new thrombus formation (arterial) that may lead to skin necrosis, gangrene of extremities, myocardial infarction, pulmonary embolism, stroke, and death.

Sodium citrate has been in widespread use as an anticoagulant for stored blood for more than 70 years. Systemic administration of citrate has, until recently, only been associated with the transfusion of blood products. In the last decade, sodium citrate has been evaluated as an alternative to heparin anticoagulation in high-risk patients undergoing hemodialysis. The regional use of citrate has resulted in successful anticoagulation of the dialysis assembly without systemic anticoagulation of the patient. Similarly, citrate is used for regional anticoagulation for patients undergoing various types of pheresis. Citrate exerts anticoagulant activity by chelating calcium into a soluble complex. Because calcium is an integral ion involved in the clotting cascade, local removal by citrate prevents the activation of clotting cofactors, factor X, and prothrombin, and the ultimate formation of fibrin.

Citrate is a normal metabolite of the Krebs cycle and is rapidly metabolized and excreted by the kidneys. In patients with normal renal and hepatic function, removal from the blood is rapid enough to prevent systemic anticoagulation. Adverse effects attributed to the administration of citrate have occurred primarily during multiple rapid blood transfusions (greater than or equal to 1 U every 3 to 4 min in a 70-kg person). Paresthesias, nausea, muscle cramps, and tetany have been reported along with hypotension, decreased cardiac output, and a prolonged QT interval. Because of the rapid rate of metabolism of citrate, these effects are thought to be a consequence of the rate of infusion as opposed to the actual amount of citrate administered. Use in regional anticoagulation has not been associated with such effects. No standard concentration of sodium citrate solutions for arterial catheter flushing has been established. The only concentration for this use described in the literature is a 1.4 percent solution in 0.9 percent sodium chloride. The amount of sodium citrate administered with this solution during a 24-h period is 1.5 g when the flush solution is infusing at 3 ml/h. In comparison, this is approximately equal to the amount of citrate administered with 40 ml of whole blood, but much less than the 15-g sodium citrate doses administered for regional anticoagulation during hemodialysis.

**Table 3—Effect of Heparin and Citrate on Coagulation Chemistry Values**

<table>
<thead>
<tr>
<th>Hour</th>
<th>Site*</th>
<th>1.4% Sodium Citrate</th>
<th>Heparin, 4 U/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PT, s</td>
<td>APTT, s</td>
<td>PT, s</td>
</tr>
<tr>
<td>0</td>
<td>V</td>
<td>24.3 ± 4.0</td>
<td>12.9 ± 1.8</td>
</tr>
<tr>
<td>24</td>
<td>V</td>
<td>23.7 ± 3.9</td>
<td>12.6 ± 1.2</td>
</tr>
<tr>
<td>0</td>
<td>C</td>
<td>24.1 ± 3.5</td>
<td>12.9 ± 1.9</td>
</tr>
<tr>
<td>24</td>
<td>C</td>
<td>24.1 ± 3.8</td>
<td>12.8 ± 1.6</td>
</tr>
</tbody>
</table>

*Site refers to location of blood collection. V = vein; C = catheter.
ysis.

Because of the relatively small amount of citrate administered during the study period, adverse effects are unlikely, and in fact, none was observed. The sodium citrate solution had no effect on serum ionized calcium. Laboratory studies revealed no effect of citrate or heparin on systemic coagulation. Additionally, collection of accurate coagulation chemistry values from the arterial catheter was not affected by either flush solution.

Because of the small number of patients in this investigation (n = 40), the results must be considered preliminary. Analysis of the data reveals that the investigation had sufficient power to detect differences in catheter survival of 30 percent or greater. Larger studies will be needed to confirm our results.

In summary, these results suggest that 1.4 percent sodium citrate is an effective and safe alternative to heparin for routine use in peripheral arterial catheter flush solutions.

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