Vascular catheter locking solutions in rats: Sodium citrate as an alternative to heparin

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Abstract
Pharmacokinetic studies in rats are conducted using a chronically implanted catheter that allows for repeated blood sampling; however, maintaining continuous patency sets practical limits on its uses. Catheter patency is affected by factors including flushing regimen, catheter material, and choice of locking solutions. In this study, a recently introduced non-heparin based locking solution containing 4% sodium citrate was compared with traditional heparinized locking solutions with respect to their ability to maintain patency, including providing anticoagulation to vascular catheters in rats. Locking solutions of heparinized (500 IU/ml) and non-heparinized (500 IU/ml) glycerol (LOCK 2) were obtained from SAI infusion technologies. Sodium citrate (4%) with 30% glycerol (LOCK 3) was supplied by Cary Pharmaceuticals, Inc. Sixty male CD rats (Crl:CD®(SD)IGS BR) produced by Charles River Laboratories (Raleigh, N.C.) weighing 225-250 grams served as study animals. The 60 rats were randomly allocated into 3 groups consisting of 20 rats each for LOCK1, LOCK2 and LOCK3. The left caudal abdominal area, thigh and intrascapular areas were shaved and the skin prepared using Betadine. The catheter was sealed with metal plug and the external portion was tunneled subcutaneously, exiting at the inter-scapula regions. For each group, 5 catheters were removed, and the catheter was aspirated to remove the lock solution and withdraw blood. If this aspiration failed, then an attempt was made to inject saline into the catheter. If flush solution was successfully infused, a second aspiration was then made to determine if blood could be withdrawn. The catheter was sealed with a metal plug after the flush. The experimental design is described in the following categories: Patency of the catheter was classified in to the following groups: • Patent = Total number of catheters that were patent (fully and on flush). • Infuse only = Unsuccessful blood withdrawal but patent for infusion. • Non-patent = Unsuccessful blood withdrawal and infusion. Discussion
Heparinized glycerol (LOCK 2) had 100% full patency or patency after flush up to Day 21 (3 weeks). The patency rate after Day 21 fell down to 40% and to 20% by day 28. However, Sodium Citrate glycerol (LOCK 3) had 80% full patency or patency after flush up to Day 7 and then decreased to 40%-60% for the remaining time points. The patency rate of LOCK1 and LOCK2 is better than LOCK3 (p < 0.05). This data supports earlier findings (Luo et al., 2000), that Heparinized dextrose and Heparinized glycerol appear to be preferred catheter locking solutions to maintain patency in the rat. Sodium citrate locking solution may be used as an alternative, at a lower patency rate, where heparin is contraindicated or unavailable.

Table 1: Experimental Design

<table>
<thead>
<tr>
<th>Group</th>
<th>Number tested for patency at time point</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
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<td>a</td>
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<td>d</td>
<td>c</td>
<td>b</td>
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<tr>
<td>f</td>
<td>5</td>
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</tbody>
</table>

* One animal was excluded from the study in Group2d due to error made in patency test schedule.

Results
General observations: All animals remained clinically healthy throughout the study. All the animals showed similar weight gains after surgery (i.e. no difference between treatment groups, p > 0.05).

Materials and Methods
Lock Solutions
Heparinized dextrose (LOCK 1). Sodium heparin (10000 IU/ml) was added to 50% dextrose solution to make a final concentration of 500 IU/ml. Lock solution was purchased from SAI infusion technologies. Heparinized glycerol (LOCK 2): Sodium heparin (10000 IU/ml) was added to glycerol solution to make a final concentration of 500 IU/ml. Lock solution was purchased from SAI infusion technologies. Sodium Citrate glycerol (LOCK 3): This is a 4% sodium citrate and 30% glycerol with pH adjusted to 6.2 (range 6.0 to 6.5) with citric acid. This was provided by the supplier, Cary Pharmaceuticals Inc.

Catheter Patency
Heparinized Dextrose (LOCK 1) 7 Days 14 Days 21 Days 28 Days Total

Fully (5/5) (4/5) (4/5) (4/5) (3/20)

On flush (5/5) (5/5) (5/5) (2/5) (14/20)

Infuse only (5/5) (5/5) (5/5) (2/20)

Non-Patent (0/5) (0/5) (0/5) (0/20)

Heparinized Glycerol (LOCK 2) 7 Days 14 Days 21 Days 28 Days Total

Fully (5/5) (5/5) (5/5) (1/4) (13/20)

On flush (5/5) (5/5) (5/5) (2/5) (15/20)

Infuse only (5/5) (5/5) (5/5) (2/20)

Non-Patent (0/5) (0/5) (0/5) (0/20)

Sodium Citrate glycerol (LOCK 3) 7 Days 14 Days 21 Days 28 Days Total

Fully (2/5) (1/5) (1/5) (1/5) (6/20)

On flush (2/5) (1/5) (1/5) (1/5) (6/20)

Infuse only (2/5) (1/5) (1/5) (2/20)

Non-Patent (0/5) (0/5) (0/5) (0/20)

Patency of the catheter was classified in to the following categories: Successful blood withdrawal on first attempt.

Fully = Successful blood withdrawal on first attempt.

On Flush = Successful blood withdrawal after flushing solution into catheter.

Infuse only = Unsuccessful blood withdrawal but patent for infusion.

Non-patent = Unsuccessful blood withdrawal and infusion.