Comparison of Catheter Lock Solutions in Rats

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Introduction

Pharmacokinetic studies in rats are most effectively and humanely done using a chronically implanted catheter that allows repeated blood sampling. Once a catheter is successfully implanted, the amount of time that it reliably remains patent, with or without flushing, will set practical limits on its uses. The patency life can be affected by many factors including flushing regimen, catheter material, and lock solutions used to fill the lumen of the catheter. A number of catheter materials have been studied and their advantages and disadvantages described.

There are very few reports on the effectiveness of lock solutions and flushing regimens in maintaining patency in catheters of any construction. Heparinized saline (10-1000 IU/ML) is the most common lock solution used (1). Heparinized polyvinylpyrrolidone (PVP) has increased viscosity as compared to saline (3). Heparinized dextrose has also been used because of its increased viscosity (6). The use of heparinized glycerol as a catheter lock solution has been suggested based on empirical observations but has not been rigorously evaluated.

This study was designed to compare these lock solutions with respect to their ability to maintain patency of unmanipulated, indwelling polyurethane vascular catheters in rats. In answering questions about the suitability of lock solutions in extending patency, the use of a vascular flushing regimen would impose an unwanted variable that could confound interpretation. For this reason, regular flushing was not considered in the design of this study.

Materials and Methods

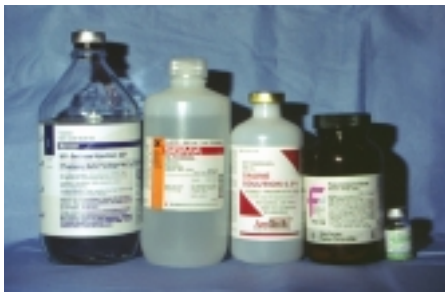
Lock Solutions

Heparinized Saline: Sodium heparin (10000 IU/ml) was added to physiological saline (0.9%) to make a final concentration of 500 IU/ml.

Heparinized Dextrose: Sodium heparin (10000 IU/ml) was added to 50% dextrose solution to make a final concentration of 500 IU/ml.

Heparinized PVP: Sodium heparin (10000 IU/ml) and polyvinylpyrrolidone (SIGMA #PVP-40) was added to physiological saline (0.9%) to make a final concentration of 500 IU heparin/ml and 1 g PVP/ml in the final solution.

Heparinized Glycerol: Sodium heparin (10000 IU/ml) was added to a glycerol solution (1.26 g/ml) to make a solution with a final concentration of 500 IU/ml of heparin.



Animals

Eighty male CD rats (Crl:CD®(SD)IGS BR) produced by Charles River Laboratories (Raleigh, N.C.) weighing between 245 and 255 grams were used. They were maintained in polycarbonate cages in a dedicated rodent surgical complex that was kept at 21 ± 2ºC with a relative humidity of 60 ± 5% and a 12/12 hour light/dark cycle. Commercially produced, sterilized feed, bedding and water were provided ad libitum. All conditions of animal preparation and use were in accordance with recommendations set forth in the Guide for the Care and Use of Laboratory Animals. The animals were of a VAF® health status.

Surgical Procedure

The animals were anesthetized with ketamine (43 mg/kg) and xylazine (8.7 mg/kg) administered intraperitoneally. The left caudal abdominal area and thigh were shaved and the skin prepared using iodine (Betadine) and alcohol. A 2 centimeter cranial-caudal incision was made to expose the femoral vein. The vein was isolated and tied off distally using non-absorbable suture material. A small incision was made in the femoral vein and a polyurethane catheter was inserted into the vein and a ligature subsequently tied around the cannulated vessel to fix the catheter in place. The catheter was locked with one of the lock solutions under study. The end of the catheter was sealed with a nylon plug. The extravascular portion of the catheter was buried under the skin of the thigh for terminal retrieval and evaluation.

Experimental Design

The 80 rats were randomly allocated into 4 groups consisting of 20 rats each. Patency of the catheter was checked for five animals within each lock solution group at 7, 14, 21 and 28 days post-implantation. At each time point, the five animals were euthanized

and the catheter located. The extravascular portion of the catheter was examined for reflux of blood and for any visible evidence of clotting. A 1 cc syringe with a blunted 23 gauge needle filled with 0.5 cc of saline was attached to the catheter after the plug was removed. The catheter was aspirated to determine the ability to remove the lock solution and withdraw blood. If the first aspiration failed, then an attempt was made to inject saline into the catheter. If flush solution could be infused, a second aspiration was then made to determine if blood could be withdrawn.

The patency of the catheter was classified in the following categories:

- Fully Patent: Successful withdrawal on first attempt
- Patent: Successful withdrawal after infusion of saline
- Non-Patent: Unsuccessful withdrawal without and with attempted infusion of saline

A necropsy was performed on those animals in which catheters had lost patency to ascertain if a mechanical obstruction or gross evidence of infection was present.

Results

Gross Observations

Lock Solution	Catheter Days	Status Types	Observation
Saline	7	Patent	Diffused blood in catheter
	7	Non-patent	2/3 of tubing filled with diffused blood
	14	Patent	Diffused blood in entire catheter
	14	Non-patent	Not applicable
	21	Patent	Diffused blood in entire catheter
	21	Non-patent	Diffused blood in entire catheter; thrombi in tips of 2 catheters
	28	Patent	Diffused blood in entire catheter
	28	Non-patent	Diffused blood in entire catheter; thrombi in tips of 2 catheters
Dextrose	7	Patent	2 catheters 2/3 filled with diffused blood
	7	Non-patent	Not applicable
	14	Patent	Filled with diffused blood
	14	Non-patent	Not applicable
	21	Patent	Filled with diffused blood
	21	Non-patent	Not applicable
	28	Patent	Filled with diffused blood
	28	Non-patent	Diffused blood in catheter; thrombi in tips of catheters
Glycerol	7	Patent	No findings
	7	Non-patent	Not applicable
	14	Patent	No findings
	14	Non-patent	Not applicable
	21	Patent	No findings
	21	Non-patent	Not applicable
	28	Patent	No findings
	28	Non-patent	Not applicable
PVP	7	Patent	Solution clear – a few small clots
	7	Non-patent	Not applicable
	14	Patent	Small hard clots in catheters
	14	Non-patent	Small hard clots in lock solution, tips covered by thrombi
	21	Patent	Small hard clots in solution
	21	Non-patent	Small hard clots in solution; thrombi in tip of catheter
	28	Patent	Small hard clots in solution
	28	Non-patent	Not applicable

Not applicable: None were non-patent.
No finding: Solution appeared clear and there were no obstructions found.

Catheter Patency

Heparinized Saline	**7 Days**	**14 Days**	**21 Days**	**28 Days**	**Total**
Patent	4/5	5/5	3/5	3/5	15/20
Fully	(4/5)	(1/5)	(1/5)	(0/5)	(6/20)
On Flush	(0/5)	(4/5)	(2/5)	(3/5)	(9/20)
Non-patent	1/5	0/5	2/5	2/5	5/20
Heparinized Dextrose	**7 Days**	**14 Days**	**21 Days**	**28 Days**	**Total**
Patent	5/5	5/5	5/5	4/5	19/20
Fully	(4/5)	(3/5)	(3/5)	(1/5)	(11/20)
On Flush	(1/5)	(2/5)	(2/5)	(3/5)	(8/20)
Non-patent	0/5	0/5	0/5	1/5	1/20
Heparinized Glycerol	**7 Days**	**14 Days**	**21 Days**	**28 Days**	**Total**
Patent	5/5	5/5	5/5	5/5	20/20
Fully	(5/5)	(4/5)	(4/5)	(3/5)	(16/20)
On Flush	(0/5)	(1/5)	(1/5)	(2/5)	(4/20)
Non-patent	0/5	0/5	0/5	0/5	0/20
Heparinized PVP	**7 Days**	**14 Days**	**21 Days**	**28 Days**	**Total**
Patent	5/5	3/5	4/5	5/5	12/20
Fully	(5/5)	(1/5)	(1/5)	(0/5)	(7/20)
On Flush	(0/5)	(2/5)	(3/5)	(5/5)	(10/20)
Non-patent	0/5	2/5	1/5	0/5	3/20

Fully = Fully patent on first attempt at withdrawal
On Flush = Patent after flushing solution into catheter
Patent = Total number of catheters that were patent (fully and on flush)
Non-patent = Total number of catheters that were not patent
Total = Sum of all catheters in that category

Discussion

Both heparinized dextrose and heparinized glycerol were the most desirable lock solutions from the overall patency standpoint at each time period. The heparinized glycerol lock solution had a much higher rate of fully patent catheters at all time points as compared to the heparinized dextrose group. This would be of importance if a regular dosing, sampling or flushing regimen was carried out over multiple days or weeks. The presence of diffused blood in the catheters of heparinized dextrose group at all time periods is troublesome and may provide the opportunity for microthrombi to form which were not evaluated by this study. The absence of any diffused blood in the heparinized glycerol group provides some indication that perhaps conditions for the formation of microthrombi may not be present, making this lock solution more suitable for multiple sampling purposes.

Results of this study indicate that increased viscosity of catheter lock solutions do not necessarily yield longer patency. Heparinized glycerol appears to outperform other lock solutions under the conditions of this study. In addition, the increased risk of introduction of thrombi into the circulation, the poor patency characteristics, as well as the difficulty in handling a heparinized PVP solution that is very viscous, makes it the least desirable lock solution; although, from a patency standpoint, heparinized saline is also a relatively undesirable choice.

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