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Title: Low dose heparin lock (1000U/mL) maintains tunnelled haemodialysis catheter patency when compared with high dose heparin (5000U/mL) - A randomised controlled trial

Running head: Heparin Lock Concentration

Ginger Chu,¹ Gemma M. Fogarty,² Leanne F. Avis,³ Shauna Bergin,⁴ Patrick McElduff,⁵ Alastair H. Gillies,⁶ Peter Choi⁷

¹ RN, MN, Clinical Nurse Consultant, Nephrology Department, Medical & Interventional Services, John Hunter Hospital, Hunter New England Local Health District; Conjoint Senior Lecturer, University of Newcastle, New South Wales, Australia

² RN, MN, Clinical Nurse Unit Manager, Department of Nephrology, Medical & Interventional Services, John Hunter Hospital, Hunter New England Local Health District

³ RN, Clinical Nurse Specialist, Department of Nephrology, Medical & Interventional Services, John Hunter Hospital, Hunter New England Local Health District

⁴ RN, MN, Clinical Nurse Specialist, Department of Nephrology, Medical & Interventional Services, John Hunter Hospital, Hunter New England Local Health District

⁵ BMath, PhD, Professor of Biostatistics, School of Medicine and Public Health, University of Newcastle

⁶ MB, ChB, PhD, FRACP, Senior Staff Nephrologist, Department of Nephrology, Medical & Interventional Services, John Hunter Hospital, Hunter New England Local Health District
Conjoint Associate Professor, University of Newcastle, New South Wales, Australia

⁷ MB, BChir, PhD, FRCP, FRACP, Director, Department of Nephrology, Medical & Interventional Services, John Hunter Hospital, Hunter New England Local Health District

Corresponding author: G. Chu, RN, MN, Address: 1 a Dudley Road, Charlestown NSW 2290, Australia

Telephone: (02) 49048815 Facsimile: (02) 49048820 Email:
ginger.chu@hnehealth.nsw.gov.au

AUTHOR CONTRIBUTIONS

Conception and design: GC, AG

Analysis and interpretation: GC, PC

Data collection: GC, SB, LA, GF

Writing the article: GC, PC, GF

Final approval of the article: GC, LA, SB, GF, PC, AG, PM

Statistical analysis: PM

Overall responsibility: GC

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Abstract

Background: Heparin is commonly used after haemodialysis treatments as a locking solution to prevent catheter thrombosis. The comparative efficacy and safety of different heparin concentrations to maintain catheter patency has been previously reported in retrospective studies. We conducted a prospective, randomised, controlled study of 1000U/mL heparin (low dose) vs 5000U/mL heparin (high dose) locking solution to maintain patency of tunnelled catheters.

Methods: 100 patients receiving chronic, unit-based haemodialysis with newly placed tunnelled haemodialysis catheters (less than 1 week) were randomly assigned to either a low dose (n=48) or high dose heparin (n=52). The primary intention-to-treat analysis examined time to malfunction in both groups over a 90 day period. A secondary analysis compared baseline patient characteristics in relation to catheter malfunction.

Results: Overall rate of catheter patency loss was 32% of catheters by 90 days. There was no significant difference in time to malfunction of catheters locked with low dose or high dose heparin ($p=0.5770$). Time to catheter malfunction was not associated with diabetic, hypertensive or smoking status. There was no difference in mean delivered blood flow rate, venous and arterial pressure, and dialysis adequacy between low dose and high dose groups. No patient suffered a haemorrhagic complication requiring hospitalisation during the study period.

Conclusion: Low dose heparin is adequate to maintain tunnelled haemodialysis catheter patency when compared with high dose heparin. The study also suggests that there is no relationship between catheter malfunction and diabetic, hypertensive or smoking status.

Keywords: heparin lock, catheter lock, haemodialysis, tunnelled catheter, catheter patency.

Introduction

The use of a tunneled central venous catheter (CVC) for haemodialysis access is necessary when no permanent vascular access is available. While tunneled CVCs provide quick and easy access for patients to receive haemodialysis, they are strongly associated with complications such as infection and thrombosis, which can lead to poor blood flow and inadequate dialysis.¹⁻

³ In an attempt to prevent catheter thrombosis and infection, the most common practice is to lock the catheter lumens with an anticoagulant or antibiotic solution between dialysis treatments.⁴

Heparin is the anticoagulant most commonly used to prevent catheter thrombosis.⁵ Heparin concentrations used for locking haemodialysis catheters have ranged from 1000 to 10,000 units per mL⁶ with the assumption that higher concentrations will decrease proportionally the risk of catheter thrombosis. High concentration heparin however, was also found to cause an elevated systemic activated partial thromboplastin time (APTT) and was linked with increased risk of bleeding, infection and increased cost.⁷⁻¹⁶ Chronic kidney disease (CKD) is already an independent risk factor for bleeding¹⁷; so it is important to ensure dialysis patients' exposure to inappropriate anticoagulation is minimised. To date, due to lack of randomised controlled trials of different heparin concentrations, there is no evidence-based consensus as to the most appropriate heparin lock concentration which will maintain the optimal balance of the catheter patency and the risk of adverse outcome and complications related to catheter thrombosis.

We therefore conducted a prospective, randomised controlled trial to compare the efficacies of the most commonly used heparin concentrations in Australia (1000U/mL vs 5000U/mL) in preventing catheter malfunction. We also evaluated patient characteristics associated with catheter malfunction

Materials and Methods

Study design

A 3-month prospective two-group randomised controlled trial (RCT) was conducted in one in-hospital dialysis unit and four community dialysis units, all following the same policy for catheter management. A 3-month monitoring period was selected because the average survival time of catheters within the department at the time of the study was approximately 90 days. The primary study endpoint was time to catheter dysfunction or failure.

The inclusion criteria were: age over 18 years and receiving haemodialysis; ability to provide informed consent; insertion of a new tunnelled dialysis catheter including jugular, subclavian and femoral catheters within 7 days and used exclusively for haemodialysis. The exclusion criteria were: patients with clinical requirement for a locking solution other than heparin; patients dialysed at home. We collected baseline characteristics including age, diabetic, hypertension, peripheral vascular disease, coronary heart disease and smoking status.

A protocol for managing dysfunctional catheters and a standardised treatment sheet were developed and implemented at commencement of the trial.¹⁸ The first line management for catheter dysfunction comprised additional saline flush (10mls). 2mgs/lumen tPA was the next step when the additional flush failed to restore the prescribed blood flow rate. The third line intervention was interventional radiology fluoroscopy with fibrin sheath stripping or catheter replacement as appropriate during the intervention. Education was provided to all nursing staff prior to the trial to ensure consistent documentation and CVC management. A senior dialysis nurse from each unit was appointed as a champion, and was responsible for communicating patient information to the project coordinator.

A dialysis treatment sheet was used by nurses to document treatment parameters; including blood flow rate (BFR), venous pressures (VP), arterial pressures (AP), dialysis adequacy (Kt/V) and condition of the catheter pre, during and post dialysis treatment. Each treatment

sheet was scanned into the individual patient's file. The electronic file was then used to obtain information related to catheter patency.

The prescribed BFR in our unit is between 200-350mL/min. Therefore, instead of following the National Kidney Foundation-Dialysis Outcome Quality Initiative (NKF-KDOQI) definition of catheter dysfunction as BFR <300mL/min, we defined catheter malfunction as occluded catheter lumen, or the requirement for any extra manipulation of the catheter during the haemodialysis treatment to maintain the prescribed BFR.¹⁹ Extra manipulation included use of additional non-protocol normal saline flushing or instillation of tissue plasminogen activator (tPA) into the catheter lumens. Data that was related to catheter patency such as dialysis BFRs, VP, AP and dialysis adequacy were also collected during the time of trial to provide objective data for catheter performance. Dialysis adequacy was measured by single pool Kt/V (spKt/V) calculated by Fresenius 4008 or 5008 dialysis machine (Fresenius Medical Care Australia, Smithfield NSW) post dialysis. VP and AP were expressed as an average over the dialysis treatment. These data was initially documented by dialysis nurses on the standardised treatment chart and further analysed by the project team by reviewing the monthly average for 3 month.

This study was approved by Hunter New England Research Ethics & Governance Unit (HNE Human Research Ethics approval: 12/02/12/5.05)

Study population and clinical practice

Our nephrology service provides care for approximately 250 in-hospital and satellite haemodialysis patients. At the time of study there were approximately 100 patients being dialysed via a tunnelled CVC. All catheters in the study were inserted by credentialed

interventional radiologists at the study centre, using *Arrow Cannon II plus* (Teleflex Medical Australia, Mascot NSW) retrograde split-tip catheters. All insertions were performed identically by locally approved method. Catheters were initially locked with 5000U/mL heparin after insertion and capped with a Tego[®] needlefree haemodialysis connector (Teleflex Medical Australia, Mascot NSW) after the first dialysis treatment. Patients were recruited within 3 days after a new catheter insertion, and randomised before the end of first dialysis session. Suitable participants were divided into two groups using a randomised block design stratified by dialysis unit. Patients received the allocated heparin lock dose at the end of first study dialysis treatment, and continued the same dose for a 3 month period. The control group used the default (current) treatment, 5000U/mL heparin, while the experimental group used 1000U/mL heparin. All dialysis treatments were provided via Fresenius 4008 or 5008 dialysis machines (Fresenius Medical Care Australia, Smithfield NSW), using FX80, 100 or 120 dialysers (Fresenius Medical Care Australia, Smithfield NSW)

A total of 100 patients (N=100) were recruited, Forty eight patients (n=48) were assigned into the low dose group and fifty two patients (n=52) were assigned into the high dose group.

Data analysis

The independent variable was the concentration of heparin and the dependent variable was catheter survival days. Data analysis was performed according to intention to treat. Catheter survival days were counted from the day of insertion to the day of malfunction, as defined above. The difference of catheter survival between the two groups was analysed using Kaplan-Meier survival curves (Figure 1). The different characteristics between the two groups were analysed using non-parametric *t*-test (Table 1). The same method was used to examine the data related to clinical outcome between the two groups (Table 2). The difference in time to

malfunction in each variable was analysed using Cox Regression - Breslow method for ties (Table 3).

Results

One hundred patients were randomised into two groups of 48 and 52 patients who received 1000U/mL and 5000U/mL heparin respectively. The two groups were similar in terms of age, catheter insertion site, warfarin and antiplatelet agent use, and cumulative heparin dose on dialysis. The internal jugular vein was the main insertion site for all patients in the two groups and accounted for majority of the insertions (98%). Numbers of previous catheters, history of diabetes, peripheral vascular disease were also similar and reflected the general dialysis population of the study units (Table 1). However, the low dose group had a higher proportion of patients with a history of hypertension (90%) compared with the high dose group (54%). The low dose group also contained a higher proportion of patients with prior coronary heart disease (42% vs 23%) and active smokers (29% vs 10%) compared to the high dose group.

The overall rate of catheter dysfunction at 90 days was approximately 32%. During the trial period, there were 13 vs 19 catheter failure events in the low dose vs high dose group respectively. There was no detectable difference in time to malfunction between the low dose and high dose heparin groups ($p=0.5770$) (Figure 1). In the low dose group, 7, 4, and 2 catheter dysfunction events were treated by additional normal saline flush, tPA infusion and catheter removal respectively. In the high dose group, 16, 2, and 1 catheter dysfunction events were similarly treated respectively. During the study period, there were 3 bacteraemia episodes in the low dose group and 1 in the high dose group, but no catheter was removed due to infection. No exit site infections were observed during the study period.

Catheter performance during the entire study period, in relation to BFR, VP, AP, and dialysis adequacy did not differ between the two groups (Table 2). The same parameters did not differ between the two groups when analysis was censored at the time of catheter dysfunction. There were no episodes of hospitalisation due to bleeding observed during the trial period. Prior to the trial, when high dose heparin was the default treatment, there were two episodes of hospitalisation due to a bleeding exit site and gastrointestinal haemorrhage observed in a 30 day period. Retrospective chart review of the period between catheter insertion and day 3 study recruitment revealed no difference in the rate of post catheter insertion bleeding complications (1 vs 2 exit site bleeds in the low vs high dose group respectively), and no exit site bleed require treatment other than manual pressure.

We analysed catheter dysfunction by variable. After adjusting for age, there was no significant difference in time to malfunction between diabetic and non-diabetic patients ($p=0.695$); between hypertensive and non-hypertensive patients ($p=0.134$); patients with and without peripheral vascular disease ($p=0.527$); patients with and without a history of coronary heart disease ($p=0.407$). There was no significant difference between smokers and non-smokers ($p=0.072$), and patients with low dose and high dose heparin lock (Table 3).

Discussion

The primary finding of this prospective RCT is that time to dysfunction of newly-inserted tunnelled central venous catheters was similar in patients receiving 1000U/mL and 5000U/mL Heparin lock solutions. The secondary finding is that time to catheter malfunction was not associated with diabetic, hypertensive or smoking status.

Sixty percent of Australian patients commence dialysis with a tunnelled CVC and 13% of these patients will continue to use a CVC as their permanent primary haemodialysis access.²⁰ Studies from other countries suggest that CVC use is an international problem.²¹ The establishment of

clinical processes to minimise initiation of haemodialysis with non-permanent access should be a major goal of renal services. However, the prevalence of CVC complications has warranted investigation of more suitable locking solutions to improve patient outcome and decrease associated health care cost when the use of a CVC is inevitable.

The optimum strength of heparin locking solution is not known despite its widespread use. Kidney Disease Improving Global Outcomes (KDIGO), NKF-KDOQI, European Renal Best Practice Guidelines and Caring for Australasians with Renal Impairment (CARI) do not make recommendations and there is conflicting published data surrounding this subject.^{14-16,22,23}

Several recent studies have compared different heparin concentrations as CVC locking solutions using different methodologies and with different endpoints.^{14-16,22,23} Holley *et al* performed a small, uncontrolled retrospective study with tPA administration as a surrogate measure for catheter patency, and found that low dose heparin lock was associated with higher tPA usage.¹⁴ In contrast, Thompson *et al* and Thomas *et al* found no difference in catheter malfunction between low dose (1000U/mL) and high dose (10000U/mL) heparin lock concentrations.^{16,22} Thomas and colleagues' study enrolled a high number of patients but the two treatment groups were not treated at the same time.²² Maya *et al* performed a retrospective analysis of 105 patients and demonstrated no difference in catheter patency between heparin lock concentrations of 1000U/mL and 5000U/mL.²³

Yevzlin and co-workers performed a retrospective study of 1000U/mL vs 5000U/mL heparin lock solutions with a safety endpoint, and found the higher dose was significantly associated with major bleeding complications, as defined by a need for escalating level of care.¹⁵ A similar result was noted in the study of Thompson and colleagues, and elevated APTT was identified in patients who received high dose (5000U/mL) compared with low dose (1000U/mL).¹⁶ In the studies of Thomas *et al* and Maya *et al*, safety of heparin locks was evaluated as a secondary

outcome and no difference in major bleeding complication or hospital admission was noted.

22,23

This study was therefore configured as a prospective RCT of 1000U/mL vs 5000U/mL heparin in newly inserted tunnelled catheters. Prevalent catheters were excluded. The strengths of this study include its robust, randomised methodology, and the high rates of data collection achieved for its pre-specified parameters. To the best of our knowledge, this study is the first prospective RCT comparing different heparin concentrations on catheter patency within a dialysis population. The study used a functional endpoint for catheter patency, defined by the need for clinical interventions to maintain the prescribed dialysis BFR for individual patients.²⁴ BFR itself was not used in our study as the endpoint, to avoid the confounding effect of prescribed BFR reductions due to non-catheter-related influences such as intercurrent infection and intravascular volume depletion. The study by Moist et al similarly advocated against the use of BFR as an outcome measure for catheter function.²⁴

The limitations of this study include differences between the study and control groups, short follow-up period and size of study population. The two randomised groups were not similar with respect to the incidence of prior hypertension, coronary artery disease and active smoking. However, these differences would plausibly favour increased catheter loss in the 1000U/mL group, thus magnifying disadvantage of the experimental group. In fact, sub-analysis suggested these baseline characteristics did not contribute to catheter loss (Table 3). In addition, this study only observed patients for 3 months; this being the average time that tunnelled CVCs were used in our department at the time of study design. Napalkov et al demonstrated that the catheter-related complications is highest in the first 90 days of catheter placement, hence the 3-month study period is adequate to identify the efficacy of the intervention.²⁵ However, given that some tunnelled CVCs are used for a long period of time, it is possible that a longer observation period might have revealed differences in the long-term efficacy and safety of low

vs high concentration heparin locks. The clinical application of such data should be set in the context of an overall imperative to reduce long-term tunnelled catheter use. Another limitation of this single-centre study is the sample size of 100 patients. This represents 95% of the eligible patient pool, but the study did not have significant power to detect small differences in catheter failure rates between groups. However, the finding that the numerical rate of catheter failure was higher in the 5000U/mL group compared to the 1000U/mL group at study termination suggests that the study conclusion was not overly influenced by the sample size. A larger prospective multi-centre trial will be required to validate the result of this study.

Conclusion

Low dose heparin is adequate to maintain tunnelled haemodialysis catheter patency when compared with high dose heparin. Based on potential risks associated with using high dose heparin lock, we recommend consideration of low dose heparin locking solution for haemodialysis CVCs. These findings need to be definitively confirmed by a larger prospective RCT.

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Figure Legends

Figure 1. Kaplan-Meier curve of time to malfunction for low dose (1000U/mL) and high dose (5000U/mL) heparin groups. P=0.57.

Table 1. Demographic and baseline characteristics of patients. Age is expressed as mean (and standard deviation). Categorical variables were compared by Chi square test, and continuous variables were compared by non-parametric *t*-test. Significance was defined as p value < 0.05.

	Dose of Heparin		P Value
	Low dose	High dose	
	(N=48)	(N=52)	
Age (years)	62 ± 18.3	62 ± 17.0	NS
Catheter site (%)			
Internal Jugular	47 (98%)	52 (98%)	NS
Left	8 (17%)	4 (8%)	NS
Right	39 (81%)	47 (90%)	NS
Femoral	1 (2%)	1 (2%)	NS
# patients on Warfarin (%)	4 (8%)	4 (8%)	NS
# patients on Antiplatelet agents (%)	19 (40%)	22 (42%)	NS
# patients had previous catheters (%)	16 (33%)	23 (44%)	NS
≤2	10 (21%)	14 (27%)	NS
>2	6 (12%)	9 (17%)	NS
median cumulative heparin (loading + infusion)	2000 units	2000 units	NS
Diabetes (%)	23 (48%)	32 (61%)	NS
Hypertension (%)	43 (90%)	28 (54%)	0.0001
Peripheral Vascular Disease (%)	13 (27%)	13 (25%)	NS
Coronary Heart Disease (%)	20 (42%)	11 (23%)	0.0312
Current Smoker (%)	14 (29%)	5 (10%)	0.0254

Table 2. Clinical outcome using low dose (1000U/mL) and high dose (5000U/mL) heparin lock concentrations, displayed as median values (and standard deviation). Groups were compared by non-parametric *t* -test, with threshold for significance defined as p value <0.05.

Clinical Outcome	Dose of Heparin		P Value
	Low dose (N=48)	High dose (N=52)	
Venous Pressure (mmHg)	110 ± 15.7	119 ± 21.9	NS
Arterial Pressure (mmHg)	-114 ± 18.3	-125 ± 23.5	NS
BFR (ml/min)	245 ± 21.8	252 ± 23.7	NS
Kt/V	1.28 ± 0.14	1.32 ± 0.27	NS
# patients with tPA (%)	4 (8%)	2 (4%)	NS
#patients with additional normal saline flush	7 (15%)	16 (30%)	NS

Table 3. The contribution of variable to loss of tunnelled catheter patency. Cox regression with Breslow method for ties was used to examine presence of diabetes; hypertension; peripheral vascular

disease; coronary heart disease; and smoking status. Threshold for significance was defined as p value <0.05.

Variable	Number (%)	Hazard Ratio	P Value
	malfunction	(95%CI)	
Diabetes	18 (33%)	0.87 (0.43-1.76)	NS
Hypertension	21 (30%)	0.54 (0.24-1.2)	NS
Peripheral Vascular Disease	8 (32%)	0.77 (0.33-1.75)	NS
Coronary Heart Disease	8 (26%)	0.68 (0.28-1.68)	NS
Current smoker	3(17%)	0.33 (0.096-1.10)	NS
Low dose heparin	13 (27%)	0.81 (0.40- 1.65)	NS