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Intradialytic Heparin Reduction & Validation of Extracorporeal Circuit Subjective Clotting Scale Study

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Intradialytic Heparin Reduction & Validation of Extracorporeal Circuit Subjective Clotting Scale Study

by

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Abstract

Unfractionated heparin (UFH) use during dialysis has a narrow therapeutic window; if misjudged the dose administered by nurses based on visual assessment of post dialysis clotting and hemostasis time can cause adverse bleeding or ill effects in these patients. The purpose of this MN thesis prospective study was to examine the efficacy of a new heparin protocol. Specific research questions included: 1) Will the use of a more aggressive heparin-reduction protocol reduce the cumulative heparin dosage in chronic hemodialysis (HD) patients, 2) Is there a relationship between the dialyzer clotting scale and the ultrasound based FBV measurement, and 3) Is the visual dialyzer clotting scale used for the study reliable?

Use of the study protocol significantly reduced cumulative heparin dose ($p=<0.001$); without affecting KT/V ($F(5,55)=1.67$, $p=.157$) or leading to extracorporeal circuit loss. Inter-rater reliability was evident between study nurse dialyzer scores ($p=0.688$) but there was no intra-rater reliability between study nurse and or clinical nurse educator/hemodialysis nurses.

Acknowledgements

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This thesis is dedicated to my family. Mama and Papa, you have provided me with immeasurable love and support and instilled the love for education and always striving for excellence. Rippan, your constant encouragement has been wonderful and comforting. Sunny, you are always going to be part of my life and I dedicate this to your loving memory.

To Iesha and Naveena, my beautiful and precious daughters, I could not imagine my life without you. You have taught me to live in the moment and remind me of what is important in my life.

But most importantly, to my husband. I have leaned on you most heavily, yet you have stood by my side, supported me and allowed me to reach for the stars and my dreams. You have guided me through my failures and celebrated my successes. Your unfaltering faith in me has kept me going in the most difficult times.

“You never change things by fighting the existing reality.

To change something, build a new model that makes the existing model obsolete.”

— Richard Buckminster Fuller

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List of Abbreviations

Abbreviation	Definition
ACT	Activated clotting time
AD	Acetic acid dialysate
ANOVA	Analysis of variance
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
B2MG	Beta 2 microglobulin
CD	Citric acid dialysate
CHREB	Conjoint health research ethics board
CKD	Chronic kidney failure
CRP	C reactive protein
CSN	Canadian Society of Nephrology
CVC	Central venous catheter
CVVHD	Continuous Venovenous Hemodialysis
EPO	Erythropoietin
ESA	Erythropoietin stimulating hormone
ESRD	End stage renal dialysis
FDA	Food and drug administration
FBV	Fibre bundle volume
GFR	Glomerular filtration rate
HD	Hemodialysis
HIT	Heparin induced thrombocytopenia
ID	Identification
INR	International normalized ratio
IV	Intravenous
KDOQI	Kidney Dialysis Outcome Quality Initiative
LMWH	Low molecular weight heparin
LVH	Left ventricular hypertrophy
MDRD	Modification of diet in renal disease
NKF	National Kidney Foundation
PD	Peritoneal dialysis
PTH	Parathyroid hormone
PTT	Partial thromboplastin time
RRT	Renal replacement therapy
SARP	Southern Alberta Renal Program
SHPT	Secondary hyperparathroidism
UFH	Unfractionated heparin

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CHAPTER ONE: Introduction

In 2012, 2.6 million Canadians were reported to have kidney disease or were at risk for kidney disease (The Kidney Foundation of Canada, 2012). The number of patients undergoing treatment for kidney failure and the number of Canadians living with End Stage Kidney Disease (ESKD)[1] has tripled since 1990, with 38,000 Canadians in 2009 being affected (Canadian Institute for Health Information, January 20, 2011). The Kidney Foundation of Canada (2012) reports that 39,352 people are currently being treated for kidney failure in Canada and 59% of these patients are on dialysis. Researchers have presented statistics which indicate that 54% of those who initiated renal replacement therapy (RRT) in 2009 were age 65 years of age and older, compared to 33% in 1990. As well, prevalence rates of RRT have increased by over 500% in the 75 years of age and older group (Canadian Institute for Health Information, January 20, 2011). This may lead to a need for increased social and health care support due to the chronicity of the disease.

Brown (2000) reported that hemodialysis patients aged 70 years of age or above had twice as many co-morbid conditions compared to younger patients. The increase in the number of elderly patients on dialysis may well lead to increased costs for healthcare due to increased co-morbidities in this population. For instance, in comparing older dialysis patients to age, race, and gender-matched patients without renal disease, Brown (2000) noted that there was greater functional disability and increased need for healthcare and social services among the dialysis patients.

Currently, there is no cure for Stage 5 kidney disease; available treatment options include renal replacement therapies, that is, transplantation, peritoneal dialysis (PD), hemodialysis (HD),

[1] End-stage kidney disease is the complete or almost complete failure of the kidneys to function.

or conservative management. Due to the limited number of donor kidneys available for transplantation, dialysis (HD and PD) tends to be most common method of treatment (National Kidney Foundation, 2002). Hemodialysis is a lifesaving treatment for patients with Stage 5 Chronic Kidney disease (National Kidney Foundation, 2002) and is the most prominent renal replacement therapy used in the Southern Alberta Renal Program; in March 2012, the SARP data analyst reported 703 intermittent HD cases, 245 PD and 462 transplant cases (C. Zhong, personal communication, March 07, 2012).

Hemodialysis treatment is provided either in the community or in a hospital setting depending on medical stability of the patient. Chronic maintenance HD treatment involves the patient dialyzing three times a week for four hours per treatment. In addition to adherence to the HD treatment schedule, patients are required to follow strict diet (low potassium, low phosphorus, and low sodium) and fluid restrictions. Typically, HD patients also have multiple co-morbidities such as cardiovascular disease, metabolic abnormalities, malnutrition, inflammation, anemia, and bone disease, making their medical management very complex (Mailloux & Henrich 2012). Due to the complexity of renal disease, mortality rates for of dialysis patient is 25% at one year and 60% at 5 years (Davison, 2011).

In addition to the burden of medically complex health management needs as their renal disease progresses, HD patients experience additional burden related to the chronic and extensive nature of HD treatment. Patients have to rely on the HD machine to live and regard it as their lifeline; they also report that the time consuming and tiring dependence on the HD machine disrupts marital, family, and social life (Hagren, Pettersen, Severinsson, Lützén, & Clyne, 2002; Polaschek, 2003). Davison (2011) reports that dialysis patients have a huge disease burden and the number and severity of their symptoms, including pain, anorexia, anxiety, and depression, are comparable to those of many cancer patients. Furthermore, hemodialysis therapy does not relieve the patients of all the symptoms of renal failure. For example, more than half of hemodialysis patients are reported to experience pronounced fatigue and lack of energy (Hagren et al., 2002). Hemodialysis patients experience continuing symptoms of end stage renal disease (ESRD) and side effects of dialysis which may include a general lack of energy, insomnia, pruritis, restless legs, hypotension, and general malaise following treatment (Polaschek, 2003). Therefore, the hemodialysis patient has ongoing struggles and challenges in management of their renal failure. Adding to this complexity is the need to manage anticoagulation during hemodialysis.

1.1 Anticoagulation during Hemodialysis

Hemodialysis treatment has advanced over the past several decades; improvements in dialysis machines and equipment make regular dialysis more efficient and tolerable for patients. Despite these technologic advances, patients continue to experience the ongoing problem of clot formation when their blood is exposed to the dialysis machine tubing or dialyzer.

Unfractionated heparin (UFH) is the most common anticoagulant used during hemodialysis to prevent clotting and is currently used in the SARP (Appendix B). Unfractionated heparin can however, have negative systemic effects for the patient such as increased bleeding risks due to underlying uremic platelet dysfunction and anticoagulation during hemodialysis continues to be a challenge (Evenepoel et al., 2002; Ross, 2011). In the SARP, nurses use a specific heparin protocol (Appendix B) to manage anticoagulation during hemodialysis. This protocol is described below.

1.2 Southern Alberta Renal Program (SARP) Intradialytic Heparin Protocol

Unfractionated heparin, in a concentration of 1:1000 I.U. is administered during dialysis into the bloodlines in the arterial chamber of the HD machine. Nurses typically administer UFH as a bolus at the start of treatment followed by an hourly infusion. Unfractionated heparin is administered throughout the entire duration of a HD treatment for patients with a Central Venous Catheter (CVC) but is generally discontinued in the last hour of HD for needled patients (Appendix B).

In the SARP, a nephrologist prescribes the initial intradialytic heparin dose for new patients. After initiating the heparin order, nurses (licensed practical and registered) monitor and adjust heparin dose based on the SARP policy (Appendix B). Heparin dose adjustment is not based on objective blood tests, such as partial prothrombin time (PTT) or activated clotting time (ACT); rather, two subjective criteria are used: 1) visual assessment of the dialyzer (refer to Figure 1) and 2) post-needling hemastasis time (i.e., time post dialysis needle removal for site to stop bleeding). Nurses are required to chart both of these assessments on the patient record post dialysis.

Hemodialysis nurses often struggle with intradialytic heparin adjustment and monitoring as it is based on an unvalidated subjective clotting scale, a method widely used in Canada. In current clinical practice there appears to be variability in nurses rating the dialyzer, especially when using a rating scale of ‘0’ or ‘1’. Dose reduction of heparin is only done if 3 consecutive runs on the dialyzer are rated as ‘0’ on the clotting scale (Appendix B). As well, there is no requirement for a nurse to double check with another nurse prior to making a change in heparin therapy. The data recorded is often incomplete and heparin reduction may not be undertaken, even though it may be warranted by the current policy. Nurses’ practice in relation to the SARP protocol is an important feature of nursing practice during HD that has not been studied and could potentially be affected by the results of this study.

1.3 Background of Creation of Study Heparin-Reduction Protocol

The study heparin reduction protocol was implemented as part of a study in progress that compares the effect of Citrate acid based dialysate (CD, Appendix A) and usual acetic-acid based dialysate (AD) on cumulative heparin during conventional hemodialysis (Citrasate study, Appendix C). In the context of the parent Citrasate study, questions were raised about whether one could be more aggressive in safely decreasing heparin dose than with the SARP protocol, which requires nurses to wait until three consecutive runs with a clotting score of "0" prior to reducing heparin.

The study heparin protocol was created to ensure that all study patients were treated equally with respect to heparin dose and that they were actually on the lowest heparin dose possible. The protocol involved inducing a clotting score of "2" in the dialyzer/venous chamber (see Figures 1 and 2) and then the heparin dose was increased in the following run to achieve a clotting score of 1 (i.e., few strands clotted in dialyzer or small clot in venous chamber, based on visual subjective assessment). As noted above, the clotting scale used for this rating has not been previously assessed for reliability and validity but a similar clotting scale has been reported in the literature (Sagedal et al., 2006).

Each week during the midweek HD session throughout the study period the dialyzer fiber bundle volume (FBV; see next section for a full description) was also determined at the onset of dialysis (within 30 minutes) and again prior to disconnection from dialysis by a consistent trained research nurse, using a non-invasive ultrasound dilution technique. At the end of each HD session, the research nurse photographed the dialyzer and venous chamber using a digital camera on a tripod, with standardized lighting, at a standardized distance and height of the dialyzer.

Table 1. Study Heparin-reduction Protocol for Run in Phase

Dialyzer/Venous chamber appearance at the end of each HD session	Heparin dose adjustment for next HD session
0/1: 0= clear, no clotting in dialyzer 1= Few strands/small clot	Decrease boost by 200 units and decrease running dose by 200 units/hour
2=1/2 of dialyzer clotted	Increase boost by 200 units *and* increase running dose by 200 units/ hour *then discontinue* protocol and *maintain* this new heparin dose for remainder of study phase. This dose will be the “baseline heparin dose”. *Restart* heparin protocol at the start of each study phase.
3=3/4 of dialyzer clotted (able to return blood)	Increase boost by 300 units and increase running dose by 300 units/hour
4=100% clotting of dialyzer (unable to return blood)	Increase boost by 400 units and increase running dose by 400 units/hour
Bleeding from access site post-dialysis	**Heparin dose adjustment**
Unusually prolonged for the patient	Turn off heparin 30 minutes earlier than usual and decrease running dose by 200 units/hour

0= Clear, no clotting in dialyzer 1= Few strands clotted 4 = 100% Clotted

Figure 1. Dialyzer Visual Appearance Examples

0= clear, no clotting 1= Few strands/small clot 2=1/2 clotted 3 = 3/4 Clotted

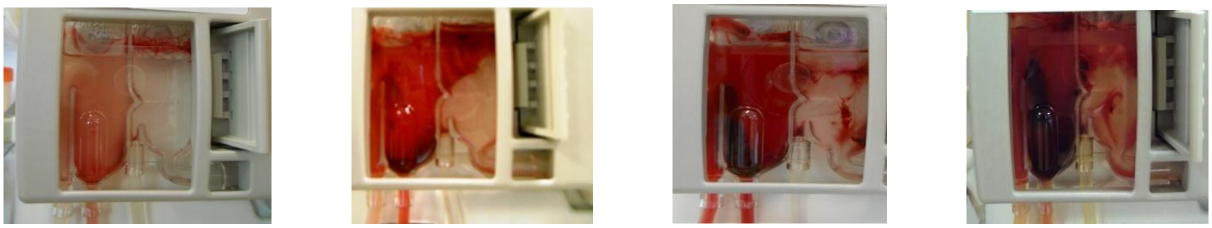

Figure 2. Venous Chamber Appearance Examples

1.3.1 Fibre Bundle Volume (FBV)

The FBV has been proposed as a more accurate and objective method of assessing the degree of clotting within the dialyzer than the current practice than the nurse-based visual clotting scale of clot burden in the dialyzer and venous chamber. The FBV is measured with a non-invasive ultrasound technique. The FBV is a measure of the volume of space within the blood compartment of the hollow fibre dialyzers; this volume decreases in the presence of clot (Krivitski et al., 1998). The FBV is a noninvasive evaluation that also provides an indirect assessment of the surface available for diffusive exchanges during hemodialysis. Two ultrasound probes are placed on the extracorporeal circuit, one on the arterial and one on the venous bloodline (before and after the dialyzer; Figure 3). A small bolus (25 ml) of normal saline is given through the arterial chamber and the FBV is determined from the transit time of this saline bolus as it passes through the dialyzer and dilutes the blood in the corresponding venous ultrasound sensor sensors (Krivitski et al., 1998). All measurements are duplicated and the mean value is the FBV, which is related to the degree of clotting in the dialyzer.

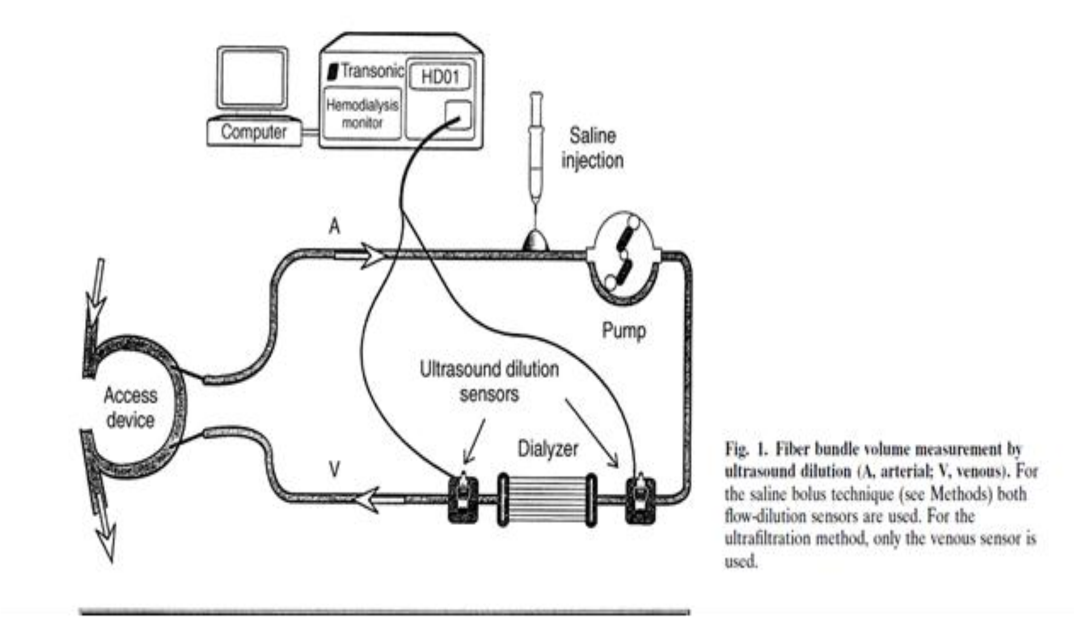

Figure 3. FBV illustration (Krivitski et al., 1998)

1.3.2 Ethnographic Study Results

In an attempt to gain greater understanding of heparinization nursing decisions, I conducted a small ethnographic study of a community outpatient HD unit. During this study, it was observed that while nurses had theoretical knowledge of the dangers and negative consequences of heparin therapy, this knowledge did not appear to be translated to practice. They were able to tell me about problems related to bleeding or patients losing precious blood volume in the machine if they were not heparinized adequately. However, this awareness may also have made them more reluctant to decrease heparin. The nurses themselves stated that heparin is a drug that needs to be respected but due to the chronic/routine nature of their work they may be "a little lax, or we may get complacent" with respect to heparinization. The ethnographic study results highlighted the dangers of busy units and lack of adherence to protocols in practice with respect to heparin dosing during HD.

Anticoagulation practices vary widely within Canada (Appendix E) and there is currently no standard anticoagulation algorithm or clotting score scale. Due to my interest in anticoagulation I became involved in the Citrasate study. The study heparin protocol was created in an attempt to reduce heparin dosage to a minimum and became the focus of my MN thesis research.

1.4 Purpose of Study and Research Questions

The purpose of this MN thesis research was to examine the efficacy of a new heparin protocol and assess the reliability of the visual study clotting scale. Specific research questions included:

Question 1: Will the use of a more aggressive heparin-reduction protocol prevent extracorporeal circuit clotting and reduce the cumulative heparin dosage in chronic hemodialysis patients?

Question 2: Is there a relationship between the dialyzer clotting scale and the ultrasound based FBV measurement?

Question 3: Is the visual dialyzer clotting scale used for the study reliable?

1.5 Summary

In this chapter, the background to this study was introduced in relation to the parent Citrasate study and the main variables of interest are described. In Chapter two, literature is presented to increase understanding of anticoagulation in regards to HD therapy. In Chapter Three, the research design and methodology for the study is presented. In Chapter Four final findings of the study are described. Finally, in Chapter Five study results and the implication for nursing and future research direction are discussed.

CHAPTER TWO: Literature Review

In order to understand complexities inherent in HD treatment and anticoagulation, a detailed review of CKD, HD therapy, complications, standard anticoagulation therapy with unfractionated heparin and alternative anticoagulation strategies was undertaken. The literature review was restricted to adults as children were excluded from my study.

2.1 Chronic Kidney Disease (CKD)

Chronic Kidney Disease is defined as presence of kidney damage or a decreased level of kidney function for a period of three months or more, based on glomerular filtration rate (Levin et al., 2008; National Kidney Foundation, 2002)(Appendix A). According to the Canadian Society of Nephrology (CSN), CKD is estimated to affect between 1.9 million and 2.3 million Canadians (Levin et al., 2008). Levin et al. (2008) found that CKD often coexists with cardiovascular disease and diabetes and is recognized as a risk factor for all-cause mortality and cardiovascular disease. In a large community-based cohort study conducted in Alberta, Canada between the years 2003 – 2007, the risk of mortality, myocardial infarction, and progression to kidney failure with a given eGFR was found to be independently increased in patients with higher levels of proteinuria (Hemmelgarn et al., 2010). At present, CKD has been proven to be best controlled in the early stages by tight blood pressure and glycemic control (Levin et al., 2008). As per personal communication with the SARP data analyst March 2012, there are a total of 1493 patients in the CKD clinics being followed by nephrologists.

2.1.1 Stage 5 CKD

In some cases however, CKD cannot be controlled or reduced and the disease advances to the last stage of the disease, Stage 5 CKD. Stage 5 CKD is also called established chronic kidney disease and is synonymous with the now outdated terms ‘end-stage renal disease’

(ESRD) or ‘chronic kidney failure’ (CKF) (Ridley, Baker, Mills, Murray, M & Ton 2009; Wikipedia, 2012). Stage 5 CKD is permanent, irreversible, and requires renal replacement therapy for the patient to sustain life. This stage of CKD is associated with multiple negative effects on the patient: anemia, renal bone disease, nutritional impairment, neuropathy, impaired quality of life and reduced life expectancy (Freedman et al., 2005). More than 87,000 patients with stage 5 CKD die each year in the United States; the majority are elderly, with multiple co-morbidities (Davison, 2011).

2.1.2 Renal Replacement Therapy

Currently, there is no cure for Stage 5 kidney disease; treatment options available include renal replacement therapies and conservative management. Renal replacement therapies include PD, kidney transplant, or HD (Appendix A). Treatment depends on type of kidney disease, severity of kidney damage, and complications or developments of other diseases (Johnson et al., 2004).

2.2 Hemodialysis Treatment Background

Hemodialysis is a lifesaving treatment for patients with Stage 5 CKD (National Kidney Foundation, 2002). It has allowed for longer survival of patients with Stage 5 CKD, thus increasing the incidence of patients on dialysis throughout the world (Miles & Friedman as cited in Morsch, Gonçalves, & Barros, 2006). The primary goal of hemodialysis is to restore the intracellular and extracellular fluid environment that is characteristic of normal kidney function. In hemodialysis an artificial, synthetic semi- permeable membrane (dialyzer) partly does the work of kidneys to filter waste and remove extra fluid (Figure 4). The dialyzer itself is composed of thousands of tiny synthetic hollow fibers.

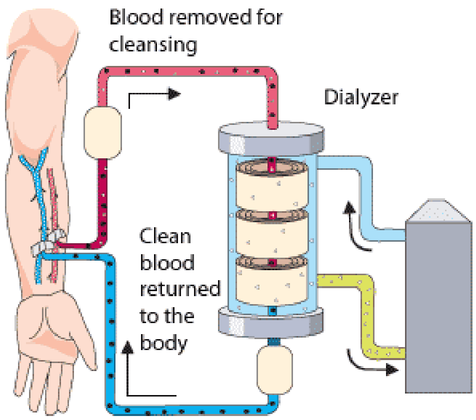

Figure 4. Hemodialysis treatment (MedBroadcast Clinical Team, 2012)

2.2.1 Dialysis

Dialysis is the removal of solutes and fluid according to their concentration gradient across a semipermeable membrane (the dialyzer). A vascular access provides adequate delivery of blood to the dialyzer fibres where dialysate flows around the outside of the fibers, while water and wastes move between these two solutions and are removed (Figure 5). The cleansed blood is then returned via the circuit back to the body. The electrolytes in the dialysis solution are also used to balance electrolytes in the patient’s blood.

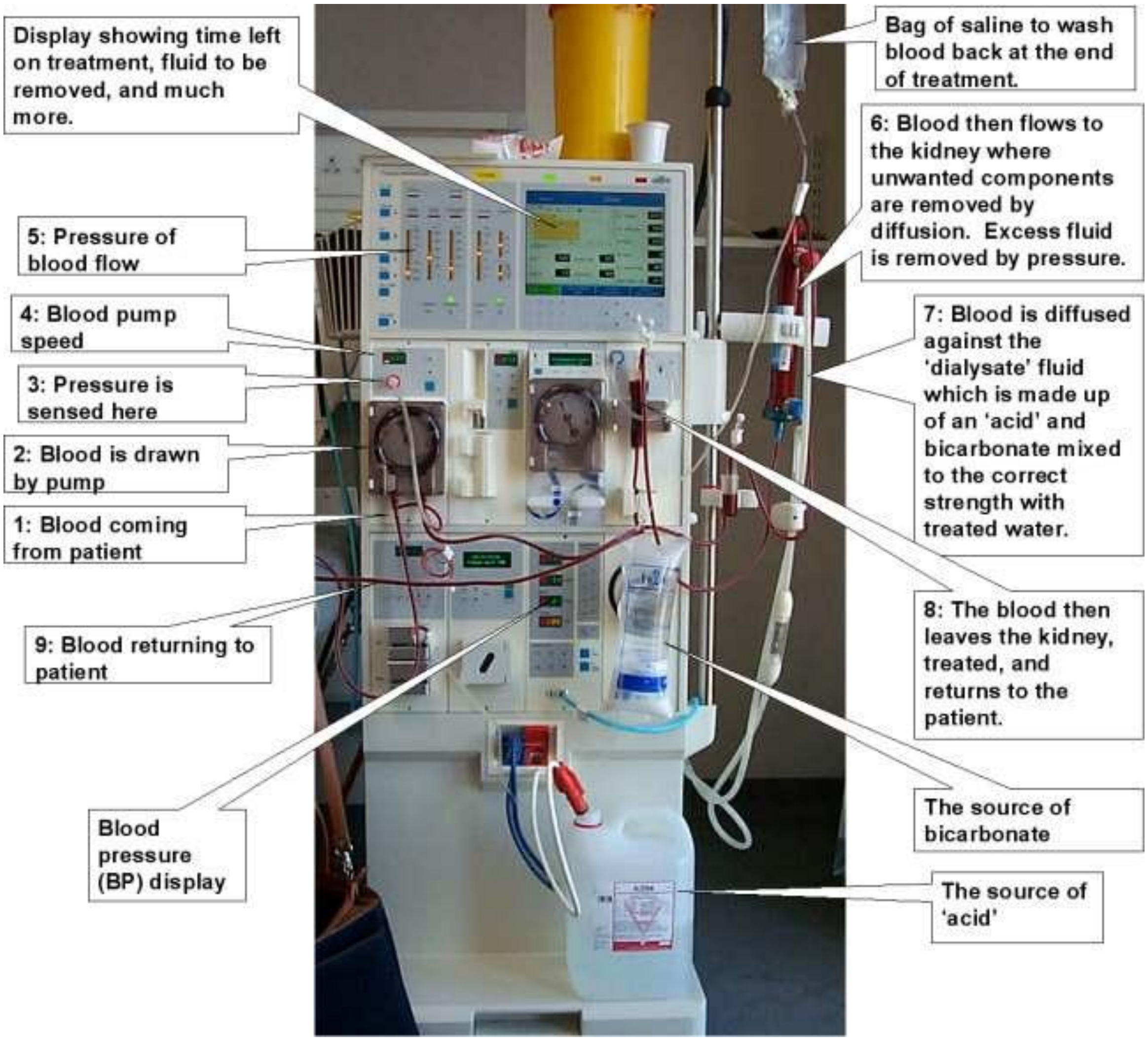

Figure 5. Hemodialysis machine (Khandekar, 2012)

2.2.2 HD Vascular Access

Chronic HD therapy requires a vascular access that can function for an extended period of time and be able to withstand the fast pump speed of the machine for maximal clearance. A functioning vascular access is critical to the patient's hemodialysis treatment and access choices include: Arteriovenous Fistula (AVF), Arteriovenous Graft (AVG), or Central Venous Catheter (CVC). Figure 6 illustrates these three types of vascular access.

2.2.3 Arterial Venous Fistula/Arterial Venous Graft

An AVF is created using a surgical connection of an artery to a vein, thereby allowing for enlargement and strengthening of the vessel in order to allow for repeated cannulation. An AVG is created using a foreign material, usually GORE-TEX®, to connect to an artery and vein. An AVF is the optimal access choice for chronic HD, as it uses the patient's native veins for fistula creation and is associated with the lowest risk of complications. When the AVF/AVG access is mature, two large bore Steele needles, #15 or #16 gauge, are inserted into the AVF/AVG prior to each HD treatment. The needles are removed post treatment and the needle site is held by either the nurse or patient to stop the bleeding. Post-treatment hemostasis time (clotting time of needling sites post needle removal) plays a critical role in heparin dose changes for these patients. This time is recorded by the nurses as part of their assessment. Sometimes clot inducing agents such as surgicel® or gelfoam® are used to speed up the hemostasis time upon the discretion of nurses.

2.2.4 Central Venous Catheter (CVC)

Some patients with failed AVF or AVG or with an urgent HD start may require CVCs for treatment. Central Venous Catheters are double lumen catheters that are inserted in the Subclavian, Internal Jugular, or Femoral vein. They tend to have the most complications such as the development of central vein stenosis (Dinwiddie & Bhola, 2010) infections, thrombosis, inadequate flow, and increased cost to maintain (Graham, Hiremath, Magner, Knoll, & Burns, 2008).

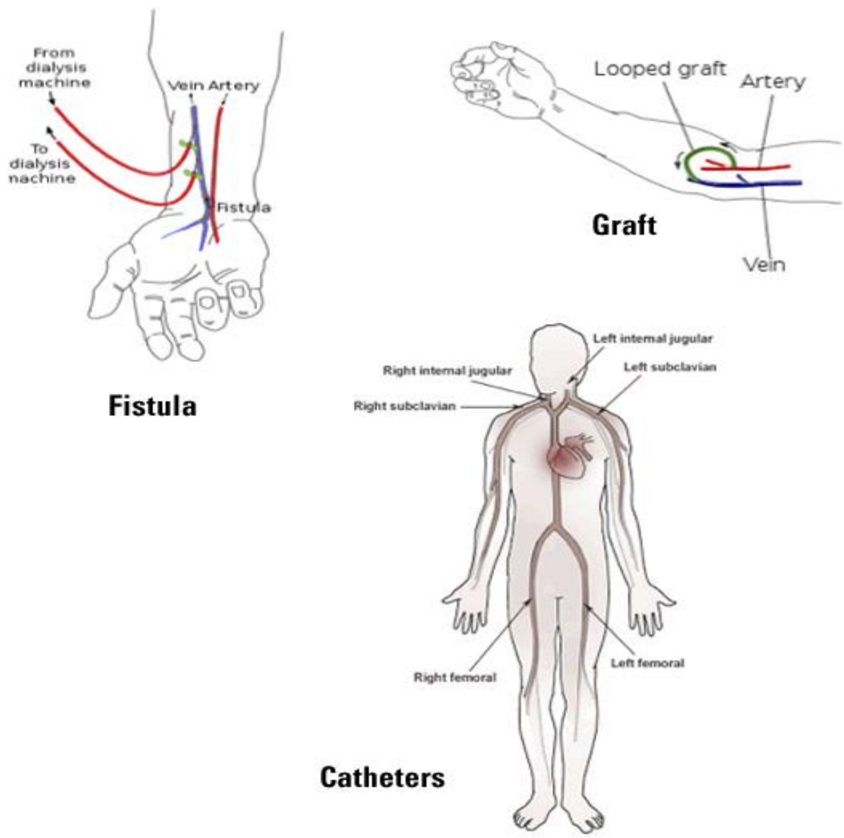

Figure 6. Types of vascular access (Centre for Disease, 2012)

2.2.5 CVC & Thrombosis Risk

Patients with CVCs can have more interruption to the blood pump compared to needled patients. As the tip of the catheter is free floating in the right atrium it is affected by patient positioning leading to HD machine pump stoppages due to arterial and venous pressure alarms. Patients with frequent interruptions to the pump speed are more prone to clotting of the bloodlines and the dialyzer. In the SARP, a CVC is locked with 4% sodium citrate solution post treatment; occasionally heparin solutions of varying concentration ranging from 1:1000 to 1:10,000 may be ordered. The CVC is the least preferred access for HD as it is associated with the highest risk of complications.

According to the Dialysis Outcome & Practice Patterns Study (DOPPS III), between the years 2005-2007, Canada had a 39% prevalence rate of CVC use compared to 33% in 2002-2003 (Ethier et al., 2008). The author attributed the high rate of CVC use to patient-specific factors such as vascular (unsuitable vessels) and medical contraindications. The SARP also has high prevalence rates for CVC use; access stats from July 2012 indicated a 42% patient prevalence rate for CVC use (J. Lee, personal communication, July 11, 2012).

2.2.6 Hemodialysis Diet & Fluid Restrictions

Standard/ conventional HD treatment, which involves dialyzing three times per week for four to five hour sessions, has largely remained the same over the years (J. Himmelfarb, 2005). As the patients do not dialyze every day, they are required to follow strict diet and fluid restrictions. HD patients generally lose their ability to produce urine (oliguria), thus are restricted to 1000ml per day of fluid intake in total (Molaison & Yadrick, 2003). Hemodialysis patients also have to restrict dietary sodium, potassium, and phosphorus based on laboratory blood chemistry results, due to the kidney's inability to excrete wastes (Molaison & Yadrick, 2003). Hemodialysis patients' blood chemistry and hematology are checked at least once a month and patients are counseled by the dietician accordingly. It is very difficult for HD patients to follow the diet recommendations and these strict diet and fluid restrictions have been shown to cause depression, anxiety, and fear in patients (Hagren, 2002 cites Griedman).

2.2.7 HD Complications

Intermittent hemodialysis patients can experience a wide range of complications due to fluid removal and electrolyte shifts during HD treatment. Most of the patients experience hypertension predialysis related to systemic fluid buildup between treatments. As the fluid is rapidly removed during HD in a condensed four-hour treatment, it can lead to hypotension.

Hypotension is the most common intradialytic problem, encountered during 5% to 40% of HD treatments (Davenport, 2006). Repetitive hypotension episodes may result in numerous small cerebral infarcts (Davenport, 2006). Hemodialysis patients also have significant risk for ischemic colitis due to repeated episodes of hypotension and hypovolemia, especially in patients with advanced atherosclerosis and compromised circulatory status (Saeed, Agrawal, Greenberg, & Holley, 2011).

Cardiovascular problems are prevalent due to excessive inter-dialytic weight gains on a thrice weekly schedule and increasing co-morbidities of an aging dialysis population. Cardiac arrhythmia is the leading cause of sudden death during dialysis, accounting for 80% of all sudden deaths (J. Himmelfarb, 2005). Main causes of this are presence of coronary artery disease and left ventricular hypertrophy (LVH), which is worsened by intradialytic hypotension (Himmelfarb, 2005).

The risk of accidental falls is very high in the HD patients due to adverse effects of treatment such as hypotension, and post treatment fatigue (Abdel-Rahman, Turgut, Turkmen, & Balogun, 2011). In a study of 219 HD patients during four year follow up, one in seven patients had suffered at least one major bone fracture requiring hospitalization which led to serious decline of the patient’s health (Kohlmeier et al., as cited in Abdel-Rahman et al., 2011). Dialysis patients are at higher risk of hip fractures than the general population (Kestenbaum & Belozeroff, 2007) and as most patients receive intradialytic heparin during HD sessions, the bleeding risk is intensified with falls or fractures.

In addition, CKD patients, especially HD patients, are at higher risk of lower gastrointestinal bleeding due to uremic platelet dysfunction, heparin use, and other anticoagulants which all contribute to anemia (Saeed et al., 2011). Fluctuations in hemoglobin are monitored closely for HD patients and affect intradialytic heparinization requirements. Changes to the hemoglobin affects heparinization during HD as high hemoglobin is associated with increased risk of clotting of the circuit. All these complications of HD may be compounded by the need for anticoagulation, typically heparin, during hemodialysis treatments itself.

2.3 Anticoagulation

In addition to the chronicity and complications of HD therapy, HD patients require anticoagulation during treatment. HD involves circulating the patient's blood in an extracorporeal (blood tubing and dialyzer) system for treatment, which initiates the clotting cascade. This extracorporeal circulation makes blood prone to clotting (Appendix D). In addition to the dialyzer and blood circuit, causes of blood clotting in a HD circuit have been identified as blood-air interface, slow flow, turbulence, hemo-concentration caused by high hematocrit, access recirculation, excessive fluid removal with inadequate vascular refilling, and blood transfusion during treatment (Black, 2008; Fischer, 2007). Signs of clotting during HD treatment may include increases in venous pressure and/or transmembrane pressure, decreases in online clearance, and darkening of blood (Black, 2008). To prevent clotting of the extracorporeal circuit, anticoagulation therapy is required (Figure 7). Inadequate anticoagulation during hemodialysis can lead to clotting of the blood in the bloodlines and the dialyzer which can subsequently lead to blood losses, decreased hemodialysis efficiency, increased nursing workload and increased cost of dialysis treatments (Richtrova, Rulcova, Mares, & Reischig, 2011; Surani & Chow, 2010).

Anticoagulation associated with hemodialysis however, continues to be a challenging issue for hemodialysis patients. Unfractionated heparin is the standard and most common anticoagulant utilized for HD. The UFH is a naturally occurring polysaccharide that works as an anticoagulant by inhibiting the activity of several blood coagulation factors and binds to antithrombin ‘‘heparin-binding factor I’’(Fischer, 2007).

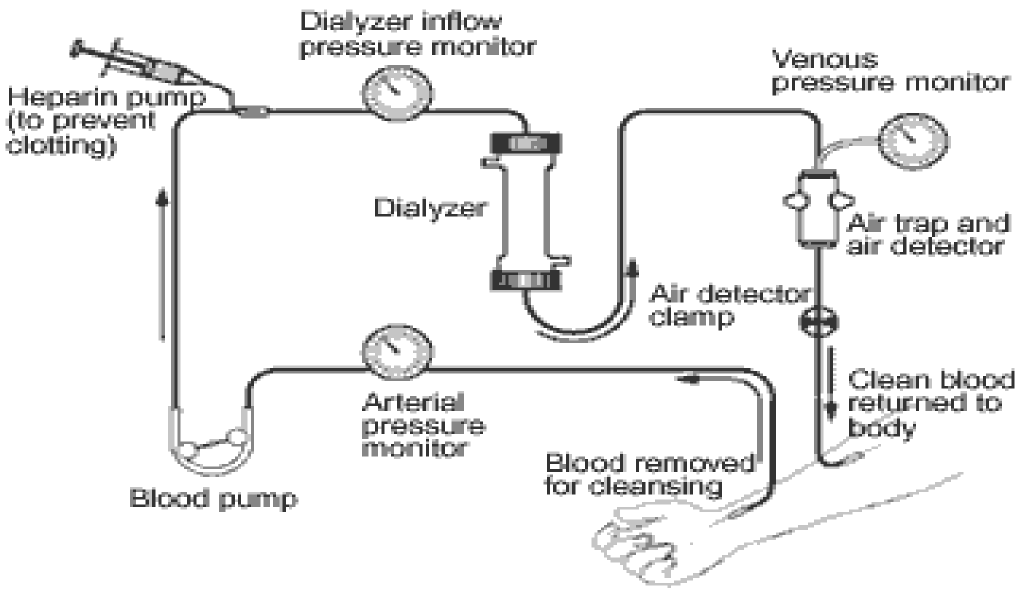

Figure 7. Heparin sequence in HD treatment diagram (National Kidney and urological diseases Information Clearhouse, 2011)

2.3.1 Heparin Safety Concerns

In 2006, a safety alert was issued by the United States (U.S.) Food and Drug Administration (FDA), warning health care professionals about heparin induced thrombocytopenia (HIT; reduction in the number of platelets in the blood) associated with intravenous (I.V.) administration of UFH and low molecular weight heparin (Advanced Renal Technologies, 2009). In 2008, significant numbers of acute sensitivity reactions associated with heparin were reported in patients undergoing dialysis in the United States (Lima et al., 2011). Lima et al. (2011) stated that these clinical events were related to heparin impurity and the major contaminant identified in the affected batches was an over-sulfated chondroitin sulfate. There were 130 reactions reported due to heparin contamination characterized by hypotension (50%), nausea (48.7%), and shortness of breath (37.5%) (Ward & Aronoff, 2010). The mean time between heparin administration and onset of reactions was 5.1 minutes. In October 2009, the U.S. FDA issued a public alert regarding unfractionated heparin related to change in potency observed in some brands of manufactured heparin. The safety issues regarding heparin usage have led to re-evaluation of anticoagulant therapy.

2.3.2 Unfractionated Heparin (UFH)

Unfractionated heparin, discovered in 1920s, was one of the main factors making HD treatment possible (Brunet et al., 2008). The UFH is used to prevent clotting of the extracorporeal (outside the body) circuit (Ahmad, Callan, Cole, & Blagg, 2005; Daugirdas, Blake, & Ing, 2006). Unfractionated heparin, part of the anticoagulant (blood thinner) family of drugs including low molecular weight heparins, helps prevent blood clots from forming.

With a half-life of about 1.5 hours, UFH is generally administered as a bolus at the start of hemodialysis treatment and then as a continuous IV infusion throughout the treatment (Sonawane, Kasbekar, & Berns, 2006). The UFH has a relatively short half-life, a low cost, and can be administered by a heparin syringe connected to the extracorporeal hemodialysis circuit (Sonawane et al., 2006). Uremic patients have increased pre-existing bleeding tendencies due to their platelet dysfunction and ineffective platelet-vessel interaction (Evenepoel et al., 2002; Ross 2011). During hemodialysis, the risk of bleeding is further intensified due to the administration of heparin, which acts by systemically anti-coagulating the patient. In fact, appropriate anticoagulation is measured by an increase in the partial thromboplastin time to 80% of the baseline values (Daugiradas, Blake & Todd, p. 207).

Since heparin provides systemic anticoagulation, it is contraindicated in certain situations such as active bleeding, trauma, pericarditis, intracerebral bleeding, thrombocytopenia, coagulopathy, diabetic retinopathy surgery and peri-operative care. Furthermore, heparin can lead to osteoporosis, pruritis, hyperkalemia, immune-mediated thrombocytopenia, vascular access related bleeding, hyperlipidemia, alopecia (hair loss) and anaphylactic reaction (Daugirdas et al., 2007; Kossmann et al., 2009; Fischer, 2007; Sonawane et al., 2006). According to Sonawane et al. (2006), ‘heparinized hemodialysis patients have higher rates of daily subclinical gastrointestinal blood losses compared with normal patients and patients with chronic kidney disease’ (p. 306). Heparin induced thrombocytopenia has also been reported to occur in up to 12% of the hemodialysis patients (O’Shea et al., 2003). Immune-mediated HIT constitutes a potentially life-threatening complication of heparin therapy, requiring an immediate switch to a non-heparin alternative anticoagulant (Fischer 2007; Reily 2003).

Davenport (2006), reported that HD patients are at increased risk of subdural and intracranial hemorrhage because of the combination of hypertension, coupled with platelet dysfunction, co-prescription of antiplatelet agents and/or oral anticoagulants, and the use of systemic anticoagulation during hemodialysis. Davenport further stated that HD patients might not only develop gastrointestinal hemorrhage but also subcapsular hepatic hematoma and retroperitoneal hemorrhage. Systemic anticoagulation may result in acute pericardial tamponade in patients with pericarditis, resulting in acute cardiac syncope (Davenport, 2006).

Although UFH is initially prescribed by a physician, nurses are responsible for monitoring and adjusting the heparin dose during HD based on patient response. In the SARP, patient response is assessed by subjective clotting scale and bleeding post needle removal. However, the visual observation scale used in the SARP has not been assessed for validity and reliability. Therefore, prior to undertaking this study, I conducted a cross country survey of heparin practices in Canada.

2.3.3 Cross Country Survey of Intradialytic Heparin Administration Guidelines

In a cross-Canada email/telephone survey, I contacted eight hemodialysis clinical nurse educators to gather information regarding intradialytic heparin protocols (Appendix E). Three of the eight respondents indicated they do not have specific heparin dose adjustment algorithm for use during HD. Only two out of eight programs conduct routine activated clotting test (ACT) testing. In addition, only three out of eight programs have clotting scales that are utilized for assessment of dialyzer and venous chambers post dialysis. The clotting scales that are being utilized in these HD units are different from one another. In the other programs subjective assessment of visual appearance of dialyzer and venous chamber is documented without use of numerical clotting scale. Nationally, nurses play an integral role in intradialytic heparin assessment and their visual subjective assessment of the dialyzer is routinely used for heparin dose adjustment. Due to lack of standard national guidelines and a reliable clotting scale there is wide variability in program guidelines related to intradialytic heparin administration and anticoagulation testing and clotting assessment.

2.3.4 Alternative to Heparin Anticoagulants

Despite issues and complications UFH continues to be the main anticoagulant used. Alternative anticoagulants to UFH are generally reserved for patients who have HIT or active bleeding. They include low molecular heparin (LMWH), regional sodium citrate, Citrasate, continuous saline infusion, heparinoids, direct thrombin inhibitors (Appendix F).

Low molecular heparin contains fragments of UFH with mean molecular weight of 5kDA and binds with antithrombin to inhibit Xa but does not inhibit thrombin activity (Ouseph & Ward, 2000). The LMWH are potent agents but have increased half-life compared to UFH thus requiring only single bolus at the start of treatment (Davenport, 2009). Monitoring of LMWH is done by measuring anti-factor Xa laboratory values (Fischer, 2007; Davenport, 2009). Also LMWH cannot be used for HIT due to extensive cross reactivity (Kovalik, 2011). Heparanoids are seldom used and there is a lack of sufficient research study evidence to support its use in HD patients.

Regional citrate anticoagulation (Appendix A) is another anticoagulant that is generally reserved for patients with HIT or patients with systemic bleeding. Limited studies have shown that regional citrate has been shown to be has effective in preventing extracorporeal clotting and also has a lower incidence of bleeding when compared to heparin (Kovalik, 2011). Regional citrate, although effective, requires extensive monitoring and increased nursing time compared to heparin anticoagulation.

Other approaches to anticoagulation during HD have been suggested and are currently being tested in clinical trials. The most promising is the Citrate dialysate (CD) as a new anticoagulation therapy that is starting to emerge as an alternative to heparin in hemodialysis. Citrasate appears to have the least amount of side effects when compared to other anticoagulants and in some studies has been shown to reduce heparin dosage (Kossman, et al., 2006, Ahmad, et al., 2006, Gabutti et al., 2009). In a descriptive study conducted by Tu and Ahmad (2000), it was shown that citrate dialysate was successfully used to prevent clotting of the extracorporeal circuit in the intensive care unit patients.

2.4 Summary

Anticoagulation of the extracorporeal circuit is required for successful HD therapy. Compared to other anticoagulant therapies, clinicians still consider UFH safer to use during HD and advise its use for most stable chronic HD patients. Although UFH is effective in preventing clotting it is associated with several side effects for patients. As intradialytic heparin is primarily based on nurses' visual subjective assessments of the extracorporeal circuit there is potential for variability in heparin dosages and the clotting scale utilized by the nurses in the SARP has thus far not been assessed for reliability. There is also potential for over-heparinization as the heparin protocol currently used by the SARP program requires nurses to decrease the heparin **only** if there are 3 consecutive runs where the dialyzer is scored as '0'. In the study protocol (also not assessed in controlled research studies), the research nurses decreased the heparin until a clotting score of '2' was obtained and then increased it the next run. Heparin use during dialysis is generally titrated on a trial and error method. There is no research evidence related to testing and reliability of heparin dosage adjustment algorithms for hemodialysis therapy.

CHAPTER THREE: Research Design and Methodology

I conducted a repeated measures observational study to examine the effect of an aggressive heparin reduction protocol on overall heparin dosage in patients undergoing hemodialysis. This study was implemented as a sub-study of a double blind crossover randomized controlled trial comparing the effect of Citrate acid based dialysate (CD) and usual acetic-acid based dialysate (AD) on cumulative heparin dose during conventional hemodialysis (Citrasate study, Appendix C).

3.1 Research Questions

In this research study, I addressed the following questions:

1. Will the use of a heparin reduction study protocol prevent extracorporeal circuit clotting and reduce the cumulative heparin dosage when compared to the current SARP protocol in chronic hemodialysis patients?

2. Is there a relationship between the visual dialyzer and venous chamber clotting scale and the transonic fibre bundle volume (FBV) measurement?

3. Is the visual dialyzer clotting scale used for the study reliable?

3.2 Definition of Study Terms

Chronic HD - Stage 5 CKD patients who are on chronic hemodialysis therapy for renal replacement and are dialyzing in the community setting three times a week.

Extracorporeal circuit- refers to the blood outside of the patient's body present in the bloodline and dialyzer; it is about 300mls of blood.

SARP heparin protocol- the policy utilized by the nurses in the Southern Alberta Renal program to adjust patient's heparin dosage during hemodialysis treatment.

Cumulative heparin dosage- total amount of heparin delivered to the patient during HD treatment, it includes bolus as well as hourly infusion. This is recorded on every patient at the end of treatment by the nurses on the hemodialysis record.

Fibre bundle volume- FBV is the space within the blood compartment of hollow fibre dialyzers which may decrease during clotting. FBV has been proposed to be a more accurate way of assessing clotting within the dialyzer instead of the current practice of nurses visualizing the dialyzer and then subjectively assigning a clotting score number.

Transonic fibre bundle volume- is the transit time of a saline bolus passing through the dialyzer, measured and recorded by ultrasound dilution sensors.

Dialyzer & venous chamber clotting scale- assignment by the nurses of a number from "0" to "4" to the dialyzer and venous chamber post-treatment based on visual appearance, which is recorded on the hemodialysis treatment record. The SARP program and study clotting scale protocols are as follows:

SARP Clotting Scale	Study Clotting Scale
0 = clear	0 = clear
1 = few strands	1 = some streaking
2 = ¼ - ½ clotted	2 = ½ clotted
3 = ¾ clotted (able to return blood)	3 = ¾ clotted
4 = completely clotted (unable to return blood)	4 = completely clotted

3.3 Description of Study Design

This was an exploratory observational study involving a subset of Citrasate Study patients (Appendix C). This sub-study was conducted during the run-in phase of the Citrasate study. The run in phase is the beginning two weeks of the study where intradialytic heparin is adjusted by the consistent study nurse based on the heparin reduction protocol (Table 1).

3.4 Sample

A convenience sample of nineteen stable chronic hemodialysis (HD) patients was used in this study. The HD units at Sheldon Chumir Centre, South Calgary Dialysis Centre, and Sunridge Dialysis Centres in Calgary were used to recruit eligible study participants. As the student investigator is the clinical nurse educator for the SARP and Dr. MacRae (committee member) is the hemodialysis nephrologist for SARP and principle investigator (PI) of the parent Citrasate study, access to participants was ensured.

3.4.1 Inclusion Criteria

- chronic stable HD patients ≥ 18 years
- HD treatment at least three times per week for 3 or more months
- currently on the standard SARP heparin protocol

3.4.2 Exclusion Criteria

- known contraindications to heparin
- heparin-free HD
- known clotting disorder
- Warfarin therapy
- dialyzing with a dysfunctional central venous catheter (blood flow rates consistently less than 300mL/min for two consecutive hemodialysis runs and/or use of a thrombolytic drug more than two times in two weeks (MacRae et al., 2005)
- vascular access dysfunction
- planned vascular access conversion or procedure during the study period

- use of high calcium dialysate
- active medical issue with potential hospitalization
- planned kidney transplant during the study period
- planned conversion of dialysis modality (peritoneal dialysis, nocturnal dialysis) during the study period
- unable to provide informed consent

3.4.3 Sample Size

Previous studies have demonstrated that intradialytic heparin dose in HD using citrate based dialysate (CD) was reduced by 30-55% (Kossman et al., 2006; and Ahmad et al., 2006). Based on preliminary data, the investigators of Citrasate study determined that the dose of intradialytic heparin was between 1000 to 5500 units per HD session in 85% of the Calgary HD population. In this local HD population, repeated measures of heparin dose in the same individual were highly correlated (intra-class correlation coefficient > 0.85), and the data distribution was reasonably normal (mean 3000 units, SD 900 units). To estimate the sample size, the following assumptions were made:

1) Effect size: change in mean of at least 1000 units (30%), from 3000 to 2000 units, effect size of 0.8 (large, based on Cohen's table of effect sizes).
2) SD of 1000 units in the two groups
3) Type II error rate 0.05
4) Power of 0.8

Using these assumptions a total of 15 patients were required to detect a relationship between the independent and dependent variables at a two-sided 0.05 significance level.

3.5 Methods

Potential patients were approached during their dialysis sessions by the hemodialysis nurses to determine patient interest in the study. A member of the research team (primary study PI and attending physician, research nurse, or student investigator) then determined patient eligibility based on inclusion/exclusion criteria. Once eligibility was confirmed, informed written consent was obtained from each participant by the research nurse.

3.5.1 Standard HD Protocol

All study patients dialyzed at least three times per week using the Phoenix dialysis machine (Hospal-Gambro, St Leonard, Quebec Canada) and Gambro bloodlines (Gambro Lundia, Lund, Sweden). All patients were maintained on their standard dialysis prescription which included: blood flow rates of 300-450 ml/min., dialysate flow rates of 500 ml/min., dialysate temperature set to - 0.5C below the patient's pre-dialysis temperature, and dialysate sodium of 137 mmol/L unless otherwise prescribed. The priming of the dialyzers was a heparin-free, standard one liter prime volume. Each patient's target weight and dialysis prescription were optimized at the study start by the physician.

3.5.2 Heparin Reduction Study Protocol

The heparin protocol was implemented during the two week run-in phase (run 2-6, run 1 was used as baseline data collection) of the Citrasate study. Each week consisted of three HD sessions for a total of six sessions during the two week study period. Intradialytic heparin dose was adjusted by a consistent research nurse[2] as per study protocol based on: a) dialyzer/venous chamber appearance, and b) prolonged bleeding of the needling sites post dialysis. The heparin dose was reduced based on clotting scores of 0/1 and increased for clotting scores 2, 3, or 4. The

[2] Consistent research nurse is defined as the same research nurse doing all heparin adjustments.

goal clotting score was 1. The heparin dose was reduced according to the study protocol (Table 1) until a clotting score of 2 and then the following run the heparin is increased back to the previous level where the score was 1.

In addition to using the heparin study protocol, dialyzer clotting was measured objectively by measuring the dialyzer Fibre Bundle volume (FBV). Each week during the midweek HD session throughout the entire Citrasate study period (4 weeks), the dialyzer FBV was determined at the onset of dialysis (within 30 minutes of HD start) and again prior to disconnection from dialysis. This was done by a research nurse using a non-invasive ultrasound dilution technique (Transonic Inc, Ithaca New York).

Under standardized conditions[3] (see Appendix I) photographs of the four quadrants of the dialyzer and venous chamber were also taken prior to auto-emptying to provide an independent, subjective assessment of clotting. Autoemptying is a procedure to empty the fluid from the dialysis circuit at the end of treatment, after the patient's blood is returned back to them and the bloodlines are disconnected from the patient. After the patients had completed the Citrasate study, their unlabelled dialyzer photographs were randomly presented to two nurses – a research nurse and an expert nurse (clinical nurse educator), for blind rescoring of clotting with the study clotting scale. Blinding of the pictures was achieved by having an independent research student select three pictures randomly from each patient and create a corresponding blinding key (Appendix I).

3.6 Data Collection Technique

Data was collected and entered on study forms by the consistent study nurse at the end of each HD run (Appendix G). Each week during the midweek HD session throughout the

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[3] Using a digital camera on a tripod, with standardized lighting, at a standardized distance and at the height of the dialyzer.

Citrasate study period (4 weeks), the dialyzer fiber bundle volume (FBV) was determined at the onset of dialysis (within 30 minutes) and again prior to disconnection from dialysis by a consistent trained research nurse, using a non-invasive ultrasound dilution technique. Training for undertaking the dialyzer FBV included receiving an overview of the transonic machine components and uses, and hands-on training with the machine with a patient. At the end of each HD session, the research nurse photographed the dialyzer and venous chamber. The dialyzer was rotated by 90 degrees for each of the four photographs, to visually capture the full circumferential view of the dialyzer. At the end of each HD session, a second HD nurse independently scored the dialyzer with the clotting scale; this score was recorded but not used for heparin dose adjustments.

3.6.1 Inter-rater and Intra-rater Reliability

To validate the dialyzer clotting scale, inter-rater and intra-rater reliability was tested using photographs of the dialyzers. Inter-rater reliability was defined as the degree to which two raters or observers, operating independently, assigned the same ratings or values for an attribute being measured or observed (Polit, Beck, & Profetto-McGrath, 2011). Inter-rater reliability was tested by comparing the clotting scores of the research nurse with the dialysis nurses' scores, as well as the clinical nurse educator and study nurse (using study clotting scale, Table 1). The study nurse and the CNE were blinded to the pictures as noted above.

Intra-rater reliability is defined as within-rater reliability. It was tested by having the consistent study nurse rescore the dialyzer pictures at 2 different time points: initial scoring and then at time 2 (August 8, 2012). The pictures were randomly selected by research student and did not have patient or dates on the pictures. Each patient's dialyzer pictures included four pictures from different angles for rating.

3.7 Statistical Analysis

All data were analyzed using IBM® SPSS® Statistics 20, (SPSS, Inc., 2011, Chicago IL, (www.spss.com). Demographic characteristics were described using frequencies, means, standard deviations and percentages as appropriate. Key baseline dialysis characteristics of the study population are presented as means and standard deviation (SD).

1. Will the use of a heparin reduction study protocol prevent extracorporeal circuit clotting and reduce the cumulative heparin dosage when compared to the current SARP protocol in chronic hemodialysis patients?

To determine if the heparin reduction protocol was more effective in reducing the heparin cumulative dose than the standard SARP protocol, measured across 6 time periods, repeated measures analysis of variance (ANOVA) was undertaken to assess mean group differences in heparin cumulative dosage. To check for % reduction in cumulative heparin, the equation: (cumulative heparin run 6 - cumulative heparin run 1)/ (cumulative heparin run 1X 100%) was used. Descriptive statistics regarding cumulative heparin dosage for each run were also obtained.

2. Is there a relationship between the visual dialyzer and venous chamber clotting scale and the transonic fibre bundle volume (FBV) measurement in run 2 and run 5?

Due to the ordinal nature of clotting scale and the numerical nature of FBV, correlation analyses using Spearman's correlation coefficients were conducted to assess the strength of relationship between the study nurse dialyzer and venous chamber clotting scores and FBV. With Spearman's correlation coefficient, data is first ranked and then correlations are applied to those ranks.

I used Wilcoxon's rank-sum test (used to look for differences between two related samples) to check for difference between the times (i.e. repeated measure) for FBV from beginning to end of the dialysis treatment (called the delta ratio) and study nurse clotting scores (Wilcoxon's test due to ordinal nature of clotting scores) (Pallant, 2010). The following equation was used to calculate delta FBV:

FBV diff 2 = (FBV post 2-FBV pre 2)*100/FBV pre 2.
FBV_diff_5 = (FBV_post_5-FBV_pre 5)*100/FBV_pre 5.

Delta FBV ratio was also correlated with hemoglobin pre, machine KT/V[4], and blood volume processed using t-tests. To show progression of clotting scores, FBV values, KT/V, and litres processed over time, a paired statistic T-was conducted between: FBV pre-run 2 with FBV pre-run 5; FBV post-run 2 and FBV post-run 5; KT/V run 2 and KT/V run 5; blood volume run 2 and blood volume run 5.

To check for group differences between study nurse dialyzer score and venous chamber clotting score with age, male/female, hypertension, diabetes, access type, type of dialyzer, and HD vintage, Mann-Witney (clotting scores comparison to gender, diabetes, hypertension) and Kruskal-Wallis (dialyzer type, access type, HD vintage) tests were done.

3. To determine reliablity of the visual dialyzer clotting scale used for the study.

Due to the ordinal nature of the variables, Friedman's test (i.e. nonparametric test corresponding to one way repeated MANOVA) was used to determine whether there was any assessor effect on the visual clotting assessments. Three assessor comparisons were drawn.

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[4] *K* - dialyzer clearance of urea; *t* - dialysis time; *V* - volume of distribution of urea, approximately equal to patient's total body water

1) Dialyzer clotting scores of the study nurse were compared to study nurse scores from original data and time 2 (after completion of study);

2) Study nurse and clinical nurse educator dialyzer scores were compared after blind randomization using study clotting score as a guide; and

3) HD staff nurse original scores (SARP policy, Appendix B) and study nurse original scores (study clotting guide, Table 1) were compared.

3.8 Ethics and Privacy

The Citrasate study received prior ethical approval and this project is the sub-study of that project (Appendix I). Ethical approval for this sub-study was obtained from the Calgary Conjoint Health Research Ethics board (CHREB), the SARP program director, as well as the unit managers. A number of steps were taken to protect the confidentiality of patient information. All patients provided written informed consent, following which they were assigned a unique study number. The master patient list containing the patient name and study ID was maintained in a locked filing cabinet in the principal investigator's office. All data forms contained the unique study ID number only, with no other personal identifying information. Data collection forms were entered into a password protected computer, with the data files maintained on the Alberta Health Services server, with standard firewall and data security measures. The working copy of the data was accessible only to the principal investigator and study personnel undertaking analyses.

CHAPTER FOUR: Results

Results from IBM® SPSS® Statistics 20 output to answer the three research questions are presented in this chapter. As well, initial data regarding demographics and key characteristics of the study population are presented.

4.1 Demographics

The study included 19 chronic HD patients from three outpatient clinics: Sheldon Chumir, South Calgary Health Center, and Northeast SunRidge Medical Center. The first 3 patients had 4 weeks of run-in, a period which was found to be too long, thus the parent Citrasate study protocol was amended and the remaining 16 patients had 2 week run-in periods (Ethics amendment, Appendix J). Demographic characteristics of the study sample are described in Table 2. Baseline hemodialysis variables are described in Table 3.

Table 2. Demographic Characteristics

Characteristics	Frequency (%) N=19
Gender:	
Male	13 (68.4)
Female	6 (31.6)
CKD Etiology:	
Diabetic Mellitus	5 (26.3)
Glomerulonephritis	2 (10.6)
Hypertension	9 (47.4)
Ischemic Nephropathy	1 (5.3)
Obstructive Uropathy	2 (10.5)
Comorbidities:	
Diabetes	11 (57.9)
Hypertension	16 (84.2)
CVD	1 (5.3)
PVD	4 (21.1)
CAD	6 (31.6)
HD Vintage	
0-5 years	12 (63.1)
5-10 years	4 (21.1)
Vascular access	
AVF	16 (84.2)
CVC	3 (15.8)
Dialyzer type:	
Rexeed 15 =1,	2 (10.5)
18=2,	2 (10.5)
21=3	5 (26.3)
25=4	10 (52.6)
HD Duration, hrs.	
3.0	1 (5.3)
4.0	15 (78.9)
4.5	2 (10.5)
5.0	1 (5.3)

*AVF:Arterialvenous fistula; CVC:Central venous catheter; PVD: Peripheral vascular disease; CVD: Cardiac vascular disease; CAD: Coronary arterial disease; CKD: Chronic kidney disease; HD Vintage: Years on HD treatment.

Table 3. Key HD baseline variables

	N	Minimum	Maximum	Mean	Std. Deviation
Age	19	36	81	59.37	13.663
Years on HD	16	1.0	7.4	3.7	1.7920193
Final KT/V run 1	17	.93	1.97	1.3376	.28680
cumulative heparin dose run 1	19	1600	6400	3739.47	1449.193
PTT (pre study)	15	20.3	119.7	33.047	24.0891
Blood processed litres run 1	18	65.6	114.2	90.750	12.3598
Hgb (pre study)	19	90	150	112.26	14.196

*HD: Hemodialysis; PTT: Partial prothrombin time; KT/V: Dialyzer urea clearance; Hgb: Hemoglobin

4.2 Study Heparin Protocol Efficacy

Objective one: Will the study heparin protocol reduce the cumulative heparin dosage compared to the current SARP protocol?

One-way repeated measure ANOVA was performed to test for the hypothesized 30% reduction in cumulative heparin dose over 6 time periods: visit 1 (baseline), and study protocol visits 2-6. There is a statistically significant run effect on cumulative heparin dose ($F(5, 90) = 6.812$, $p<0.001$) (Appendix H). Cumulative heparin dosage per each run is presented in table 4. Pairwise comparison (i.e. paired t-test) after Bonferoni adjustment shows that there was a statistically significant difference between run 1 and subsequent runs (run 1-2, p=.000; 1 vs. 3, p=.001; 1 vs. 4, p=.001; 1 vs. 5, p=.010; 1 vs. 6, p=.027) (Appendix H). The other pairwise comparisons were NOT statistically significant.

Table 4. Cumulative heparin dosage* in units

	Mean	Std. Deviation	N
Heparin dose run1	3739.4737	1449.19316	19
Heparin dose run2	2663.1579	1997.83509	19
Heparin dose run3	2242.1053	2185.63893	19
Heparin dose run4	1947.3684	2251.51021	19
Heparin dose run5	2040.5263	2048.42073	19
Heparin dose run6	2323.6842	2357.04431	19

*heparin dose=cumulative heparin dose

As well, there was only one patient with a cumulative heparin dose of less than or equal to 2000 units at baseline run 1 whereas there were 11 patients in this category at run 6 (see table 5). There was 39% reduction of cumulative heparin dose from run 1 to run 6.

Table 5. Comparison of cumulative heparin dosage for run 1 and run 6

		chd run 1 Frequency (%)	chd run 6 Frequency (%)
Valid	1.00 <=2000	1(11)	11(57.9)
	2.00 >2000	18(8)	8(42.1)
	Total	19	19

* chd1=cumulative heparin dosage run 1; chd6=cumulative heparin dosage run 6

KT/V (dialyzer clearance, Table 6)

There is NO statistically significant run effect on KT/V ($F(5, 55) = 1.671$, $p=.157$) (Appendix H) nor was there a statistically significant run effect on access hold times ($F(5, 75) = 1.391$, $p=.238$) (Appendix H).

Table 6. KT/V descriptive statistics for run 1-6

	Mean	Std. Deviation	N
ktv1	1.4000	.30683	12
ktv2	1.4075	.32384	12
ktv3	1.3408	.33337	12
ktv4	1.3492	.29623	12
ktv5	1.3008	.36862	12
ktv6	1.3492	.34650	12

*KT/V 1=run 1, baseline; KT/V2=run2, start of heparin study protocol; KT/V3=run3; KT/V4=run4; KT/V5=run5; KT/V6=run6

4.3 FBV & Clotting Scores

Objective two: Is there a relationship between the visual dialyzer and venous chamber clotting scale and the transonic fibre bundle volume (FBV) measurement?

Correlation analyses using Spearman's rank were conducted to assess the relationship between the study nurse dialyzer and venous chamber clot scores and FBV. Statistical analyses showed no relationship between FBV and study nurse clotting scores (dialyzer and venous chamber), baseline hemoglobin, KT/V, hemodialysis vintage, and HD duration, as shown in Table 7. However, there was a statistically significant correlation between delta FBV ratio run 2 with study nurse dialyzer clotting scores (r=-.611, p=.007).

Table 7. Clotting correlation for study nurse dialyzer and venous chamber scores

	Dialyzer clot score			Venous chamber score		
	Correlation coeff	N	P value	Correlation coeff	N	P value
FBV pre Run 2	0.020	19	.934	-.067	19	.784
FBV post Run2	-.276	18	.268	-.138	18	.584
DeltaFBV run 2	-.611	18	.007*	-.142	18	.574
Kt/v run2	-.299	19	.214	.078	19	.752
Hgb baseline	.042	19	.865	.226	19	.352
HD vintage	.103	16	.706	-.142	16	.599
HD duration	.404	19	.086	-.167	19	.493
FBV pre run 5	.125	18	.622	.245	18	.327
FBV post run 5	-.319	18	.198	.137	18	.589
Delta FBV run5	-.544	18	.020*	.162	18	.521
KT/V run 5	-.154	19	.528	-.134	19	.585

*fbv pre = fibre bundle volume predialysis; fbv post = fibre bundle volume postdialysis; delta fbv= delta fibre bundle volume; KT/V =machine dialyzer clearance; Hgb=hemoglobin; HD vintage=length of time on hemodialysis treatment; HD duration= number of hours on hemodialysis treatment
*p = p<0.05

Statistical analyses showed no relationship between FBV run 5 (pre and post) and study nurse clotting scores (dialyzer and venous chamber), and KT/V run 5 (see Table 7). However, there was statistically significant correlation between delta ratio FBV run 5 with study nurse dialyzer clotting scores, (r=-.544, p=.020). As the correlation coefficient was negative; this indicates that the two variables behave oppositely - when clotting score goes up (more clotting, worse), then delta FBV goes down (more clotting, worse) and vice versa.

Correlation of study nurse dialyzer score and study nurse venous chamber clotting score with following variables: age, male/female, hypertension, diabetes, access type, type of dialyzer, HD vintage was conducted using Mann-Whitney (numerical data) and Kruskal-Wallis (ordinal/categorical data) tests as appropriate. There were no correlations evident between any of the variables and clotting scores.

4.4 Reliability of Dialyzer Scores

Objective 3: Determination of reliability of visual dialyzer clotting scale used for the study.

Due to the ordinal nature of the variables, Friedman's test (i.e. nonparametric test corresponding to one way repeated MANOVA) was used to determine whether there were any assessor effects (study nurse, hemodialysis staff nurse, clinical nurse educator). Mean dialyzer clotting scores are presented in table 8 below. Statistical analysis results indicate that there was a significant assessor effect (χ^2 (48) =10.807, p=0.013, exact p=.013). Wilcoxon signed rank tests (i.e. nonparametric tests corresponding to pair t-test) were also performed. There was NO statistically significant difference between SN1 and SN2 (z=-.816, p=.414, exact p=.688), however there was a statistically significant difference between HDN & SN1 (z=-2.183, p=.029, exact p=.049), and there was also a statistically significant difference between CNE & SN1 (z=-2.673, p=.008, exact p=.013) (Appendix H).

Table 8. Dialyzer clotting mean scores

	Mean Rank
sn1	2.72
sn2	2.64
hdn	2.34
cne	2.30

*sn1=study nurse score 1; sn2=study nurse score 2; hdn=hemodialysis nurse; cne=clinical nurse educator

4.5 Summary

Key results in our data analyses included a significant reduction in cumulative heparin dose with the use of study heparin reduction protocol, significant correlations between delta FBV and study nurse clotting scores, and good intrarater reliability of dialyzer scores for the study nurse, but poor inter-rater reliability between assessors.

CHAPTER FIVE: Discussion of the Findings

5.1 Introduction

The purpose of this MN thesis research was to: 1) determine the efficacy of an aggressive heparin-reduction protocol in comparison to the standard heparin protocol used in the SARP, 2) validate the current visual clotting scale through correlation with an ultrasound-based measurement of Fibre Bundle Volume (FBV), and 3) assess the reliability of the visual dialyzer clotting scale used for the study. This chapter includes a summary and discussion of findings, scope and limitations, implications for practice and research, and conclusions from the study.

As an experienced clinical nurse educator in the SARP, I have questioned the routine use of heparin and its inherent dangers to the patients. In reviewing intradialytic heparin use, I pondered on whether the amount of heparin patients receive during HD treatments could be reduced further without any detrimental effects to the patients' treatment. I have often struggled with the subjectivity and lack of clarity around intradialytic heparin dose adjustments and whether there are other objective ways to verify subjective clotting scores. While unfractionated heparin is prescribed by a physician, it is the nurses who are responsible for monitoring and adjusting the therapy based on the patient's extracorporeal circuit and bleeding tendencies. Currently, intradialytic heparin adjustments are based on a subjective, visual nursing assessment of clotting in the dialyzer. This critical component of HD nursing practice has not yet been assessed clinically for reliability, and is poorly understood by both nurses and nephrologists.

5.2 Summary of Thesis Research Findings

5.2.1 Question 1: Efficacy of the Study Heparin Protocol

In answering the first research question around efficacy of the study heparin protocol, intradialytic heparin dosage was significantly reduced by the implementation of the study protocol, without reducing HD clearance. As expected, with use of an aggressive heparin reduction protocol, there was a significant reduction in cumulative heparin dose. Specifically, there was a statistically significant cumulative heparin dose reduction overall from run 1 to run 6 in the two week study period. While there was only one patient with a cumulative heparin dose of $\leq$ 2000 units at baseline run 1, there were 11 patients requiring $\leq$ 2000 units of heparin by run 6. Use of the study protocol demonstrated that heparin can be successfully reduced without negative impact for the patient; specifically, there was no statistically significant change in KT/V noted from beginning of study to end of study. Due to the overall reduction in heparin dose, I had also expected we might see a decline in urea clearance due to increased clotting of the dialyzer fibers. This was not evident in the results of the study.

Another important finding from the study was that during the two week study period there were no HD systems lost due to heparin reduction. Of two systems that were lost during the study period, one was due to a machine problem and another due to access problems requiring single needle HD.

5.2.2 Question 2: Dialyzer Clotting Scale and the Ultrasound-based FBV Measurement Relationship

In answering the research question regarding correlations between FBV and clotting scores, there is a correlation with the delta FBV and the clotting score evident. However, data from the FBV pre- and post-scores, when compared to the study nurse's dialyzer clotting scores, did not provide any correlations with visual dialyzer clotting scores, a finding not unexpected due to the use of different dialyzers. However, the most important outcome came when the differences in FBV scores were normalized to the pre-HD value using delta FBV. Delta FBV[5] measurements were compared to study nurse clotting scores at HD run 2 and run 5, with

[5] Delta FBV was calculated as: (FBV post – FBV pre)*100/FBV pre

statistically significant correlations for both runs found (r=-.611, p=.007; r=-.544, p=.020 respectively). This is important information; if we are able to correlate clotting scores with delta FBV, the FBV could be used as a predicator of clotting.

Currently, there are no clinical studies in HD treatment in which medical researchers have explored the role of FBV and clotting quantification. FBV measurements have only been utilized in reprocessed dialyzers and Continuous Venovenous Hemodialysis (CVVHD) (Liangos et al., 2002; Narsipur, 2004). Liangos et al. (2002) compared FBV with other markers of dialyzer function such as urea and creatinine, measured every six hours in 31 intensive care unit patients. These authors found that during CVVHD treatment in ICU patients, FBV scores decreased during the treatment but small molecule clearance for urea was not affected. In their research, FBV decreased during each 15 hour treatment but urea decline did not appear to be correlated with FBV.

5.2.3 Question 3: Reliability of the Visual Dialyzer Clotting Study Scale

In answering the third research question related to reliability of the study clotting scale, interesting results were noted. As expected, there was intra-rater reliability of study nurse clotting scores at time two testing period. This indicates reliability of the study clotting scale for the study nurse, as there was no statistically significant difference when the scores were compared to the original scores. Intra-rater reliability was anticipated due to having a consistent person scoring the dialyzer/venous chamber and also due to the extensive education provided to the consistent study nurse at the beginning of the study.

However, there was no inter-rater reliability of the study clotting scale evident when the study nurse and CNE scores were compared. Indeed, there were statistically significant differences in the dialyzer clotting scores between the HD nurse and study nurse. While differences in scoring between the HD nurse and study nurse were expected (as the study scoring scale was different from the SARP protocol and different HD nurses were involved in scoring), the dissimilar results that the CNE and study nurse scores obtained were unexpected as both individuals had utilized the study scale for scoring. This may reflect differences in training process undertaken during scoring of the scale or in familiarity with the protocol used in the study.

5.3 Limitations of Study

There are a number of important limitations to the current study that must be acknowledged. First, the results of the study may not be applicable to acute hemodialysis inpatients as only chronic outpatients were included in the study. Further research is needed to validate the study heparin protocol and FBV transonic measurement in acute HD inpatients. Second, in the study 16 of 19 patients had AVFs and this protocol has not yet been fully tested in patients with CVCs. As well, wet Rexeed dialyzers with double cassette Gambro bloodlines were used in the study. Research is needed to assess the heparin study protocol when other dialyzers are used and types of access are in place. Finally, the majority of the patients in this study dialyzed for 4-hour treatments and heparin requirements may be different for shorter or longer treatment. Most importantly, the inter-rater and intra-rater reliability was only conducted for the dialyzer scores and did not include venous chamber scores. Reliability of inter-and-intra-rater dialyzer scores therefore needs to be assessed using more stringent and inclusive assessment protocols.

5.4 Recommendations for Practice and Further Research

The results of the study demonstrate that intradialytic heparinization in HD patients can be safely reduced. Use of the study heparin protocol algorithm, based on subjective dialyzer and a venous chamber clotting scale, is a tool to guide heparin dosing during HD in the absence of objective criteria such as laboratory tests. In this study dialyzer and venous chamber scores were used to change heparin dosages. In analysis of the study data, I observed that intradialytic heparin dosing could have been reduced further if venous chamber scores were not included for heparin dosing. For example, even post-HD venous chamber scores (as assessed by the study nurse) of ‘2’ or ‘3’ did not lead to system loss during HD in the study. Therefore, it is likely that not using the venous chamber for heparin dosing will not lead to increases in system losses. However, venous chamber scoring, in HD for anticoagulation, needs to be researched further in order to validate its use.

It is recommended to replicate this study’s heparin protocol where only dialyzer clotting scores are used to see the effect on clearance and cumulative heparin dose. Intradialytic heparin can be reduced further, in the study heparin was reduced the most in run 4 when a clotting score of ‘2’ was obtained before increasing it to obtain a clotting score of ‘1’; the clearance of run 4 and run 6 did not change, as shown in table 6.

It is important to have clear and detailed policies to guide anticoagulation in conjunction with intensive education. Programs that use clotting scores should provide intensive education about clotting score interpretation in light of this study’s findings, whereby inter-rater reliability of scores was not obtained. Heparin reduction was achieved within 2 weeks using the study nurse-led protocol. It is to be noted however, that due to subjectivity and rater variability in assigning clotting scores based on a visual scale, having a consistent, trained nurse doing the scoring is recommended. This also highlights that for programs using subjective scoring, standardization of processes and nursing education is crucial. This variability with subjective clotting scores highlights the need for in-depth training for HD nurses on the use of visual clotting scales.

In absence of objective criteria to guide heparin decisions, double checking of scores is recommended until further studies are conducted that can provide evidence of the reliability of visual clotting scores. In addition, it should be emphasized in policies and guidelines that when assigning dialyzer scores, it is critical to view the dialyzer from all sides so the subjective score can be as accurate as possible.

Education is critical to the use of clotting scores and heparin protocols due to the variability of the scale as noted in this study. It should include teaching with the use of pictures, with explicit instructions regarding assignment of clotting scores. The use of video or an e-learning module that has specific patient scenarios with clear pictures would be a useful tool in teaching nurses how to use the clotting scale and heparin study protocol. This module should also include simple definitions regarding the terminology used in intradialytic heparinization.

As an experienced hemodialysis nurse and CNE, I feel that there may be interventions to assist nurses to translate their theoretical knowledge to heparin practices on the unit. It may require changes to existing HD protocols, for example highlighting the heparin assessment by adding a check box for heparin on the hemodialysis form, under pre-dialysis assessment. Current practice also entails the nurse undertaking a detailed heparin assessment during the shift changeover period, which is the busiest time on a hemodialysis unit. Instead of during the changeover period, this should be done when the double checks are completed or when they are preparing supplies for next patient, as nurses typically have more time. As patients dialyze for 4 hours, there is slow time when the nurses are monitoring the patients prior to taking them off dialysis. This would be a better time to undertake a detailed heparin assessment. As well, the assessment of previous anticoagulation documentation should be considered part of preparing supplies, in addition to the current practice.

In this study we validated the use of the FBV delta ratio as an indicator of degree of clotting. A saline bolus method was utilized for FBV reading at the beginning and end of HD treatments. FBV measurements may not be practical for all HD units given that an ultrasound dilution machine and nursing expertise to do these measurements are required. In addition, FBV measurements will add nursing time to patient care that will need to be accounted for in patient workload. However, FBV measurements currently are a useful research tool that can be used to validate future heparin protocols.

5.5 Implications and Applications for Practice

The hemodialysis patient has a huge disease burden due to chronicity of the disease and treatment, diet and fluid restrictions, and co-morbidities. The average hemodialysis patient is exposed to heparin during dialysis three times a week and a validated rigorous heparin protocol could contribute to reducing the cumulative dose of heparin. It could even lead to complete discontinuation of heparin for some patients, leading to a reduced risk of bleeding and adverse effects for the patient. In addition, a reduction in heparin dosing could lead to shorter bleeding time post-needle removal in AVF or AVG and could lead to cost savings with less heparin use.

As the HD population is also aging, reduction in heparin dosages may have even greater impact. HD patients are prone to falls due to adverse effects of treatment, leading to more frequent hospitalizations and longer length of stays, as noted previously. Reduction in heparinization may result in a decreased bleeding risk due to an accidental falls, thus reducing negative consequences to the patient. Any reduction of intradialytic heparin will likely also reduce systemic bleeding risks such as GI bleeding, stroke, retinal bleeding, and vascular access bleeding in diabetics (Sonawane et al., 2006; Daugirdas et al., 2007; Kossmann et al., 2009).

Validating subjective assessments of the dialyzer (clotting scores) with FBV may lead to transformation of hemodialysis nursing practice. The Canadian Association of Nephrology Nurses and Technologists (CANNT) should consider supporting research in this area and work on creating national anticoagulation guidelines with a standard clotting scale. It is critical to conduct future research that is able to provide rigorous testing to assess validity and reliability of the clotting scale, as have been undertaken with pain scales utilized in nursing (Ferreira-Valente, Pais-Ribeiro, & Jensen, 2011; Pagé et al., 2012). This should include sensitivity of the scale to time and should be tested with a variety of nurses, such as registered nurses and licensed practical nurses, and those with varying degrees of nursing experience. The scale should be also should be tested with a large data set.

FBV also needs to be explored further and may be used in the future instead of a subjective clotting score. As FBV measurement is part of the care for all patients in the Citrasate study, it will be explored with a larger data set of Citrasate study patients to determine if similar results to this study are obtained. Due to the lack of research into use of FBV for clotting scales, larger studies are recommended. FBV could be used in the future for anticoagulation studies as an objective measurement of clotting and could lead to the development of standardized anticoagulation guidelines.

5.6 Knowledge Dissemination

Dissemination of research findings is crucial to advancing knowledge. I plan to present my study results at nephrology and research conferences. I also plan to publish the results of this research in an appropriate nursing journal to raise awareness of this important subject. As my research was supported by the Kidney Foundation of Canada and CANNT, I will be submitting a report of my thesis research findings to these associations. I also plan to share my results with the nurses, clinical nurse educators (CNEs) and management staff from the SARP and propose changes to education around our current heparinization and clotting scores policy.

5.7 Conclusion

This study highlights the importance of anticoagulation reevaluation in HD and lack of research in this important topic. As an experienced HD nurse, I have often struggled with lack of clarity and objectivity in heparin dosing decisions. Intradialytic heparinization is a complex issue due to factors such as variability in patient characteristics, patient medications, and HD equipment. Discontinuation of ACT testing and basing heparin decisions on a subjective clotting scale has further raised questions as to current level of knowledge and nursing/nephrologist practice in this area.

Heparin is a medication that should not be administered routinely without serious consideration of its effects to the patients. Implications for nursing education include questioning current nursing practice and striving for evidence based practice. This study contributes to knowledge regarding heparinization of chronic HD patients. It highlights the need for further research in this important area, including validity and reliability of the subjective clotting scale and evaluation of objective criteria such as FBV to guide anticoagulation dosing instead of subjective clotting scores.

References

Abdel-Rahman, E., Turgut, F., Turkmen, K., & Balogun, R. (2011). Falls in elderly hemodialysis patients. *QJM, 104*(10), 829-838.

Advanced Renal Technologies. (2009). *Citrasate dialysate.* Retrieved March 5, 2011, from http://www.advancedrenaltechnologies.com/products/index.php#info

Ahmad, S., Callan, R., Cole, J., & Blagg, C. (2005). Increased dialyzer reuse with citrate dialysate. *Hemodialysis International, 9*(3), 264-267.

Black, K. (2008). Anticoagulation for haemodialysis. *Renal Society of Australasia Journal, 4*, 95.

Brunet, P., Simon, N., Opris, A., Faure, V., Lorec-Penet, A., Portugal, H., . . . Berland, Y. (2008). Pharmacodynamics of unfractionated heparin during and after a hemodialysis session. *American Journal of Kidney Diseases, 51*(5), 789-795. doi: 10.1053/j.ajkd.2007.12.040

Canadian Institute for Health Information. (January 20, 2011). *Number of Canadians living with kidney failure triples over 20 years renal transplantation saving millions in dialysis costs.* Retrieved November 10, 2011, from http://www.cihi.ca/CIHI-ext-portal/internet/en/Document/types+of+care/specialized+services/organ+replacements/RELEASE_20JAN11

Centre for Disease. *What is dialysis?* Retrieved Feb 15, 2012, from http://www.cdcare.org/what-is-dialysis/

Daugirdas, J. T., Blake, P. G., & Ing, T. S. (2006). *Handbook of dialysis.* Lippincott Williams & Wilkins.

Davenport, A. (2006). Intradialytic complications during hemodialysis. *Hemodialysis International, 10*(2), 162-167.

Davison, S. (2011). Integrating palliative care for patients with advanced chronic kidney disease. *Journal of Palliative Care, 27*(1), 53-61.

Dinwiddie, L. C., & Bhola, C. (2010). Hemodialysis catheter care: Current recommendations for nursing practice in North America. *Nephrol Nurs J, 37*(5), 507-521.

Ethier, J., Mendelssohn, D. C., Elder, S. J., Hasegawa, T., Akizawa, T., Akiba, T., . . . Pisoni, R. L. (2008). Vascular access use and outcomes: An international perspective from the dialysis outcomes and practice patterns study. *Nephrology Dialysis Transplantation, 23*(10), 3219-3226.

Evenepoel, P., Maes, B., Vanwalleghem, J., Kuypers, D., Messiaen, T., & Vanrenterghem, Y. (2002). Regional citrate anticoagulation for hemodialysis using a conventional calcium-containing dialysate. *American Journal of Kidney Diseases, 39*(2), 315-323. doi: 10.1053/ajkd.2002.30551

Ferreira-Valente, M. A., Pais-Ribeiro, J. L., & Jensen, M. P. (2011). Validity of four pain intensity rating scales. *Pain, 152*(10), 2399-2404.

Fischer, K. G. (2007). Essentials of anticoagulation in hemodialysis. *Hemodialysis International, 11*(2), 178-189.

Freedman, B. I., Volkova, N. V., Satko, S. G., Krisher, J., Jurkovitz, C., Soucie, J. M., & McClellan, W. M. (2005). Population-based screening for family history of end-stage renal disease among incident dialysis patients. *American Journal of Nephrology, 25*(6), 529-535.

Graham, J., Hiremath, S., Magner, P. O., Knoll, G. A., & Burns, K. D. (2008). Factors influencing the prevalence of central venous catheter use in a canadian haemodialysis centre. *Nephrology Dialysis Transplantation, 23*(11), 3585-3591.

Hagren, B., Pettersen, I. M., Severinsson, E., Lützén, K., & Clyne, N. (2002). The haemodialysis machine as a lifeline: Experiences of suffering from end-stage renal disease. *Journal of Advanced Nursing, 34*(2), 196-202.

Hemmelgarn, B. R., Manns, B. J., Lloyd, A., James, M. T., Klarenbach, S., Quinn, R. R., . . . Tonelli, M. (2010). Relation between kidney function, proteinuria, and adverse outcomes. *JAMA: The Journal of the American Medical Association, 303*(5), 423-429.

Himmelfarb, J., & Ikizler, T. A. (2010). Hemodialysis. *New England Journal of Medicine, 363*(19), 1833-1845.

Himmelfarb, J. (2005). Hemodialysis complications. *American Journal of Kidney Diseases, 45*(6), 1122-1131. doi: 10.1053/j.ajkd.2005.02.031

Johnson, C. A., Levey, A. S., Coresh, J., Levin, A., Lau, J., & Eknoyan, G. (2004). Clinical practice guidelines for chronic kidney disease in adults: Part I. definition, disease stages, evaluation, treatment, and risk factors. *American Family Physician, 70*(5), 869-876.

Kestenbaum, B., & Belozeroff, V. (2007). Mineral metabolism disturbances in patients with chronic kidney disease. *European Journal of Clinical Investigation, 37*(8), 607-622.

Khandekar, A. (2012). *Hemodialysis.* Retrieved Februaury 15, 2012, from http://kidneyadvice.net/Dialysis3.html

Krivitski, N. M., Kislukhin, V. V., Snyder, J. W., MacGibbon, D. R., Kuznetsova, O. A., Reasons, A. M., & Depner, T. A. (1998). In vivo measurement of hemodialyzer fiber bundle volume: Theory and validation. *Kidney International, 54*(5), 1751-1758.

Levin, A., Hemmelgarn, B., Culleton, B., Tobe, S., McFarlane, P., Ruzicka, M., . . . Madore, F. (2008). Guidelines for the management of chronic kidney disease. *Canadian Medical Association Journal, 179*(11), 1154-1162.

Liangos, O., Sakiewicz, P. G., Kanagasundaram, N. S., Hammel, J., Pajouh, M., Seifert, T., & Paganini, E. P. (2002). Dialyzer fiber bundle volume and kinetics of solute removal in continuous venovenous hemodialysis. *American Journal of Kidney Diseases, 39*(5), 1047-1053.

Lima, M. A., Rudd, T. R., de Farias, E. H. C., Ebner, L. F., Gesteira, T. F., de Souza, L. M., . . . Hoppensteadt, D. (2011). A new approach for heparin standardization: Combination of scanning UV spectroscopy, nuclear magnetic resonance and principal component analysis. *PloS One, 6*(1), e15970.

Mailloux, L.U. & Henrich, W.L. (2012). *Patient survival and maintenance dialysis.* Retrieved March 1, 2011, from http://www.uptodate.com/contents/patient-survival-and-maintenance-dialysis?source=search_result&search=patient+survival+and+maintenance+dialysis&selectedTitle=1~150

MedBroadcast Clinical Team. (2012). *Hemodialysis.* Retrieved Feb 15, 2012, from http://www.google.ca/imgres?imgurl=http://www.mediresource.com/HealthNews/images/English/LP2_8.gif&imgrefurl=http://www.medbroadcast.com/test_and_procedure_info_details.asp%3FTPid%3D8%26Type%3D1&h=300&w=300&sz=12&tbnid=7V3MFdJ2dG2GUM:&tbnh=90&tbnw=90&prev=/search%3Fq%3Dhemodialysis%2Bimages%26tbm%3Disch%26tbo%3Du&zoom=1&q=hemodialysis+images&docid=7mCIgZjuf7KAvM&hl=en&sa=X&ei=XiM8T-unDurciQLq1-3CAQ&sqi=2&ved=0CDcQ9QEwBA&dur=604

Molaison, E. F., & Yadrick, M. K. (2003). Stages of change and fluid intake in dialysis patients. *Patient Education and Counseling, 49*(1), 5-12.

Morsch, C. M., Gonçalves, L. F., & Barros, E. (2006). Health-related quality of life among haemodialysis patients–relationship with clinical indicators, morbidity and mortality. *Journal of Clinical Nursing, 15*(4), 498-504.

Narsipur, S. S. (2004). Measurement of fibre bundle volume in reprocessed dialyzers. *Clinical Nephrology, 61*(2), 130-133.

National Kidney and urological diseases Information Clearhouse. (2011). *Treatment methods for kidney failure: Hemodialysis.* Retrieved March 5, 2011, from http://kidney.niddk.nih.gov/kudiseases/pubs/hemodialysis/

National Kidney Foundation. (2002). *KDOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification.* Retrieved Feb 13, 2010, from http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p4_class_g1.htm

Pagé, M. G., Katz, J., Stinson, J., Isaac, L., Martin-Pichora, A. L., & Campbell, F. (2012). Validation of the numerical rating scale for pain intensity and unpleasantness in pediatric acute post-operative pain: Sensitivity to change over time. *The Journal of Pain,*

Pallant, J. (2010). *SPSS survival manual.* Open University Press.

Polaschek, N. (2003). Living on dialysis: Concerns of clients in a renal setting. *Journal of Advanced Nursing, 41*(1), 44-52.

Polit, D. F., Beck, C. T. L., C.G., & Profetto-McGrath, J. (2011). *Canadian essentials of nursing research* (3rd ed.). London: Lippincott Williams & Wilkins.

Richtrova, P., Rulcova, K., Mares, J., & Reischig, T. (2011). Evaluation of three different methods to prevent dialyzer clotting without causing systemic anticoagulation effect. *Artificial Organs, 35*(1), 83-88.

Ridley,J.,Baker,J., Mills,C., Murray, M., Ton,E. (2009). Chronic kidney disease: What's in a name? *Canadian Association Nephrology Nurses Journal, 19*(2), 19-22.

Ross, S. (2011). Anticoagulation in intermittent hemodialysis: Pathways, protocols, and pitfalls. *Veterinary Clinics of North America: Small Animal Practice, 41*(1), 163-175.

Saeed, F., Agrawal, N., Greenberg, E., & Holley, J. L. (2011). Lower gastrointestinal bleeding in chronic hemodialysis patients. *International Journal of Nephrology, 2011*, 272535. doi: 10.4061/2011/272535

Sagedal, S., Hartmann, A., Osnes, K., Bjornsen, S., Torremocha, J., Fauchald, P., . . . Brosstad, F. (2006). Intermittent saline flushes during haemodialysis do not alleviate coagulation and clot formation in stable patients receiving reduced doses of dalteparin. *Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association, 21*(2), 444-449. doi: 10.1093/ndt/gfi203

Sonawane, S., Kasbekar, N., & Berns, J. S. (2006). The safety of heparins in end-stage renal disease. *Seminars in Dialysis, 19*(4), 305-310. doi: 10.1111/j.1525-139X.2006.00177.x

Surani, M., & Chow, J. S. F. (2010). Review: Anticoagulation for haemodialysis. *Nephrology, 15*(4), 386-392.

Thakuria, M., Ofsthun, N. J., Mullon, C., & Diaz-Buxo, J. A. (2011). Anemia management in patients receiving chronic hemodialysis. *Seminars in Dialysis, , 24*(5) 597-602.

The Kidney Foundation of Canada. (2012). *Facing the facts.* Retrieved September 13, 2012, from http://www.kidney.ca/document.doc?id=1376

Ward, R. A., & Aronoff, G. R. (2010). Recognizing and reacting to product-related adverse events in hemodialysis. *American Journal of Kidney Diseases, 55*(1), 11-14.

Wikipedia, t. f. e. (2012). *Chronic kidney disease.* Retrieved Feb 13, 2012, from http://en.wikipedia.org/wiki/Chronic_kidney_disease

Appendix A. Glossary of Terms

Access recirculation: Hemodialysis access recirculation occurs when dialyzed blood returning through the venous needle re-enters the extracorporeal circuit through the arterial needle, rather than returning to the systemic circulation.

Anemia: reduction of red blood cells measured as hemoglobin in the blood. Anemia is common complication of CKD and develops when renal function declines to <50% due to reduced production of endogenous erythropoietin (EPO) by kidneys and due to decreased red cell survival.

Anticoagulation: prevention of blood clotting with the use of medications.

Arterial venous fistula (AVF): Vascular access that is surgically created in the patient’s arm (diverting arterial blood flow to vein) and is used for needling for hemodialysis.

Arterial venous graft (AVG): Synthetic graft material that is inserted in the patient’s arm and is then accessed with needles for hemodialysis.

Autoemptying: is a procedure to empty the fluid from the dialysis circuit (dialyzer and bloodlines) at the end of treatment after the patient’s blood is returned back to them and the bloodlines are disconnected from the patient.

Blood-air interface: interaction of air and blood in the venous chamber, the venous chamber is one thirds full so there is some empty compartment. The arterial chamber and venous chamber bubble trap have some areas where stasis of blood may be present.

Central Venous Catheter (CVC): Synthetic flexible catheter that is inserted in a large vein, generally internal jugular or femoral, that is used to access blood for HD.

Chronic Kidney Disease (CKD): It is a chronic condition in which kidneys lose their ability to filter out excess wastes, minerals, and maintain appropriate fluid balance. It has five stages based on glomerular filtration rate that is estimated using mathematical formula and using creatinine. Stage 1-more than 90 mL/min per 1.73 m^2, Stage 2- 60–89 mL/min per 1.73 m^2, Stage 3- 30–59 mL/min per 1.73 m^2, Stage 4 - 15–29 mL/min per1.73 m^2, and Stage 5- less than 15 mL/min per 1.73 m^2.

Citrate dialysate (CD): Acid concentrate that contains citric acid instead of acetic acid in the HD dialysate.

Continuous Venovenous Hemodialysis (CVVHD): The removal of waste products from the blood by using large amounts of ultrafiltration with reinfusion of sterile replacement fluid. It is a treatment reserved for critical patients, generally in critical care units, who cannot tolerate intermittent HD.

Conservative/Palliative therapy: It includes patients with Stage 5 CKD who do not start dialysis and the patients who stop dialysis. There has been increase interest and acceptance of conservative treatment for CKD patients recently.

Dialysate: mixture of electrolytes and chemicals that is used for HD. It is also referred to as dialysis fluid, dialysis solution or bath, is a solution of pure water, acid concentrate, and bicarbonate concentrate. The acid concentrate has sodium, magnesium, acetate, dextrose, and potassium. The acid concentrate and bicarbonate are mixed with the treated water to form dialysate.

End Stage Renal Disease (ESRD)/Stage 5 CKD: Last stage of irreversible kidney disease in which patient requires renal replacement therapy to survive. Stage 5 CKD is the preferred terminology.

Erythropoietin hormone (EPO): hormone produced primarily by the kidneys that stimulates red blood cell produce from bone marrow. Anemia in HD patients results from impaired production of the hormone erythropoietin by the kidneys and reduced responsiveness to erythropoietin, often in combination with absolute or functional iron deficiency.

Estimated Glomerular filtration rate (eGFR): is a measure of kidney function. The "eGFR" is an estimated value derived from a measured serum creatinine and population means for age and gender.

Extracorporeal circuit: is the blood outside of the body. The average person has about five to six liters of blood; during dialysis only 300mls of blood is outside of the body at any given time.

Excessive fluid removal with inadequate vascular refilling: When fluid is removed during hemodialysis, the osmotic pressure is increased and this prompts refilling of fluid from the interstitial space. The interstitial space is then refilled by fluid from the intracellular space. Excessive ultrafiltration with inadequate vascular refilling plays a major role in dialysis induced hypotension.

Glomerular filtration rate (GFR): is the volume of fluid filtered from the renal glomerular capillaries into Bowman's capsule per unit time and it is the most accurate indicator of glomerular function.

Hemodialysis (HD): 'Hemo' is blood and 'dialysis' is cleaning of the blood. HD refers to a procedure for removing metabolic waste products or toxic substances from the bloodstream with an artificial kidney called the dialyzer.

Hemodialysis(HD) vintage: Years on HD treatment.

Hemodialysis vascular access: Means in which patient's blood can be taken out of the body for hemodialysis treatment. It involves either use of central venous catheter or internal access in patient's arm.

Heparin- induced thrombocytopenia (HIT): reduction of platelets after exposure to heparin.

Intradialytic: occurring or carried out during hemodialysis treatment.

Intermittent hemodialysis: involves dialyzing three or four times a week with each treatment lasting about four hours each treatment.

Kidney Transplant: Renal replacement therapy that involves surgical implantation of a donor kidney. During a transplant, the surgeon places the new kidney in patient's lower abdomen and connects the artery and vein of the new kidney to the recipient's artery and vein. A patient can receive kidney donation either from a living relative or cadaver. After the transplant the patient is required to take lifelong anti-rejection medications.

KT/V: Measure of dialysis adequacy calculated from K (dialyzer clearance), T (time) and V (volume of body water in a given patient). It can be measured by laboratory urea pre-dialysis and post-dialysis tests or can be calculated by the HD machine using sodium as a marker for urea clearance. Phoenix machine KT/V values were used for this study.

Nocturnal Hemodialysis: nightly hemodialysis that is performed at patient's home while the patient sleeps.

Oliguric: Reduction of urine output, generally less than 30ml/hr. or 400mls/day.

Peritoneal dialysis (PD): Renal replacement therapy that involves daily cleaning of a patient's blood through a peritoneal catheter surgically inserted in patient's abdomen. This treatment involves a patient instilling the dialysis solution for a few hours and then draining the solution. The exchange of waste products and removal of fluid is accomplished through the peritoneal membrane. As patients perform this treatment daily they have less diet and fluid restriction compared to HD patients.

Post hemostasis time: clotting time of needling sites post needle removal.

Regional citrate: It involves the infusion of IV trisodium citrate into the arterial bloodlines and simultaneous infusion of calcium chloride solution in the venous bloodline. The Citrate binds to ionized calcium and therefore is a potent inhibitor of coagulation. Patients require calcium infusion to correct hypocalcium caused by citrate. Patient's calcium levels are monitored frequently to adjust the IV Calcium rates in these patients.

Secondary hyperparathyroidism (SPHT): refers to the excessive secretion of parathyroid hormone (PTH) by the parathyroid glands in response to hypocalcemia (low blood calcium levels) and associated hypertrophy of the glands.

Single needle HD: HD treatment that uses one needle rather than two needles due to needling problems and is generally associated with higher heparin requirements and lower dialysis efficiency(due to stop and start of the blood pump).

Slow flow: HD machine pump speed measured in ml/min, pump speed less than 250-300ml/min is generally considered to be slow flow.

Target Weight: Desired weight that is targeted for end of hemodialysis treatment after fluid is removed during HD.

Transmembrane Pressure: Pressure across the dialysis membrane that is required to remove fluid during hemodialysis.

Turbulence: high velocity and turmoil inside the blood cassette chambers due to blood flow at high speed.

Unfractionated heparin (UFH): medication used to prevent blood clotting.

Uremia: A toxic condition resulting from kidney disease in which there is retention in the bloodstream of waste products normally excreted.

Venous Pressure: Pressure measured in the venous chamber of dialysis bloodlines by a transducer.

*Note: these definitions taken or adapted from the following sources: Centre for Disease, 2012; Davison, 2011; Fisher, 2007; Himmelfarb & Ikizler, 2010; Johnson et al., 2004; National Kidney Foundation, 2002; National Kidney and urological diseases Information Clearhouse, 2011; Surani & Chow, 2010; Thakuria, Ofsthun, Mullon, & Diaz-Buxo, 2011.

Appendix B. SARP Heparin Policy

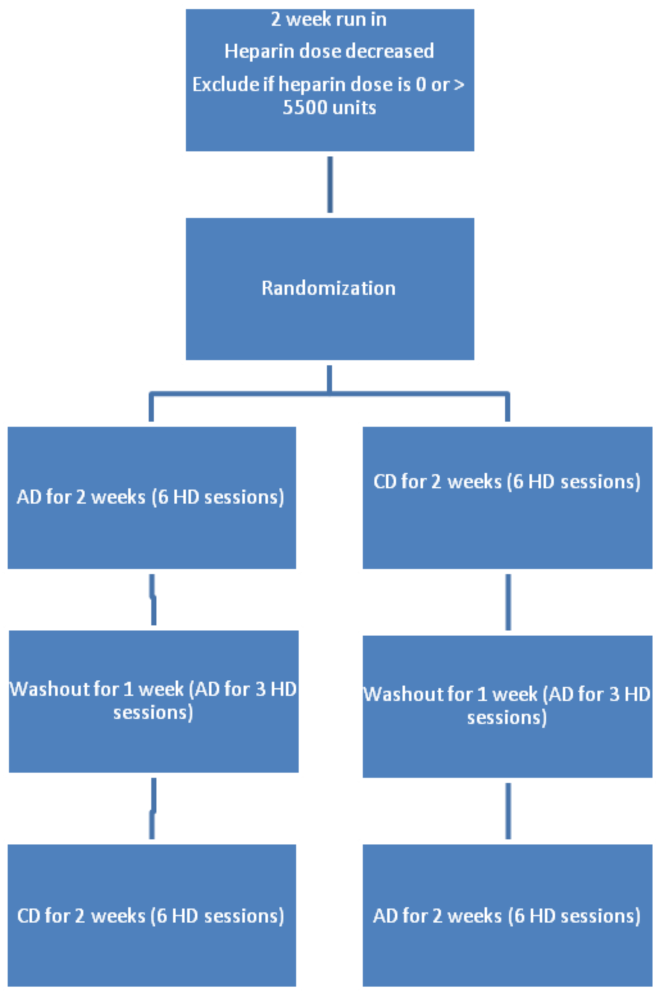
Appendix C. Citrasate Study Description

The Citrasate study is a two-period, two-treatment randomized controlled trial (RCT) with a crossover design and repeated measures. After enrolment, each patient's dose of intradialytic heparin was minimized using the study heparin protocol during a two week run-in period. The cumulative heparin dose during the last HD session of the run-in period was considered to be the baseline dose. Patients who still required intradialytic heparin after the four-week run-in period, and who still met inclusion/exclusion criteria, were randomized in a cross-over fashion to begin with either two weeks of HD with acetic acid based dialysate (AD; sequence 1) or two weeks of HD with the intervention, citric acid based dialysate (CD; sequence 2). A four-week duration was chosen to ensure adequate time to attain the minimal required dose of heparin. Patients began each study phase (intervention and control) with their baseline intradialytic heparin dose which was determined at the end of the run-in period. Nurses subsequently adjusted intradialytic heparin dose as per study protocol for the remainder of each study phase. At the end of the first study phase (two weeks) patients underwent a one-week washout period with usual AD and constant baseline heparin doses to ensure no potential for a carry-over effect. After the wash-out period, patients were crossed-over to the other treatment for the next two weeks, beginning with their baseline heparin dose. Each week consisted of three HD sessions for a total of six HD sessions for the run-in period, and 15 HD sessions for the study period, including the one-week washout.

After the two-week run-in period, study patients were randomized to one of two treatment sequences. All randomization were determined by a computer generated random number list, and concealed in opaque envelopes to ensure allocation concealment. For sequence 1, patients underwent six HD sessions over two weeks with AD, followed by a one-week washout period, followed by six HD sessions over two weeks with CD. For sequence 2, patients underwent six HD sessions over two weeks with CD, followed by a one-week washout period, followed by six HD sessions over two weeks with CD (see Citrasate study flow diagram below).

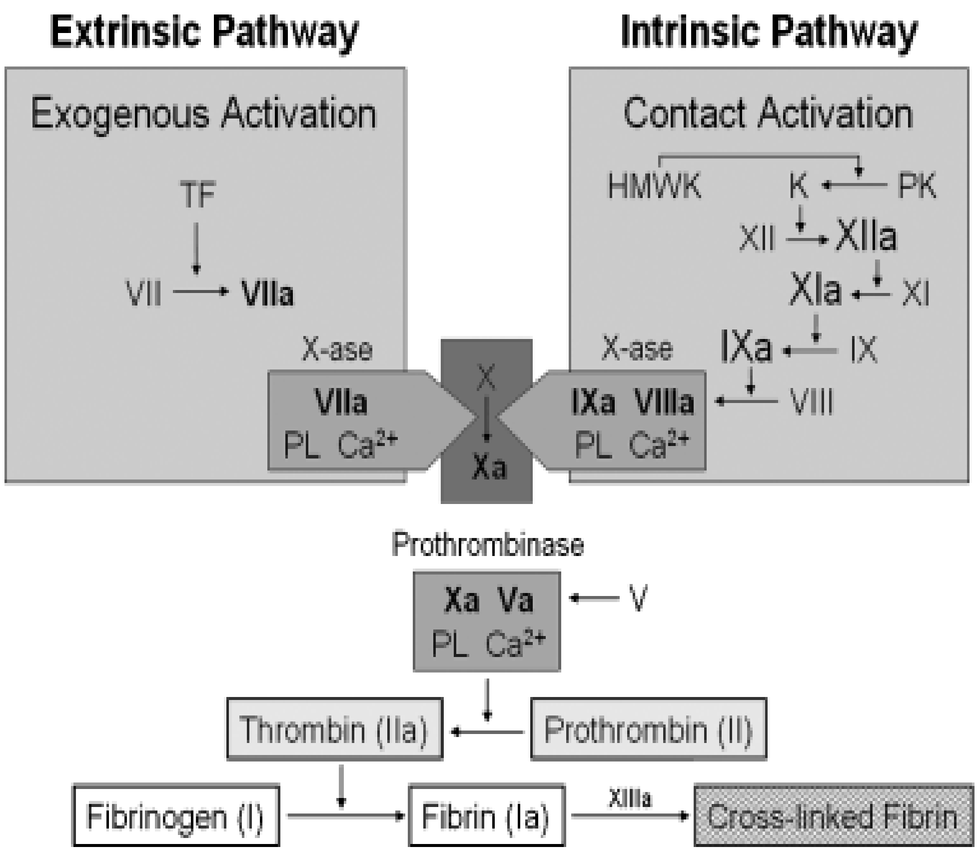
The intervention and control phases began with baseline doses of intradialytic heparin. The intradialytic heparin dose was subsequently minimized using the study heparin protocol during each HD session of each study phase. CD and AD were in identical packaging supplied by the manufacturer to ensure that investigators, patients, and health care staff were blinded.

Citrasate Study flow diagram



Appendix D. Hemodialysis & Clotting Cascade

The coagulation cascade is activated by the process of hemodialysis. The turbulent flow and shear stress activate platelets and cause platelet aggregation which in turn activates the intrinsic coagulation cascade. White blood cells are activated by the exposure of blood to the negatively charged tubing and needles and they subsequently release granules containing tissue factor which promotes factor VIIa. Other factors that are thrombogenic (promoting clots in the blood) in HD include: contact to other artificial surfaces including the dialyzer, catheters used for vascular access, arterial & venous bubble traps, interface of air & blood and the turbulences in the bubble trap. The activation of platelets, leukocytes, and the coagulation cascade leads to clotting of the dialyzer and bloodlines (Suranyi & Chow, 2010; Fischer 2007).



Clotting Cascade (Fischer, 2007, p, 179)

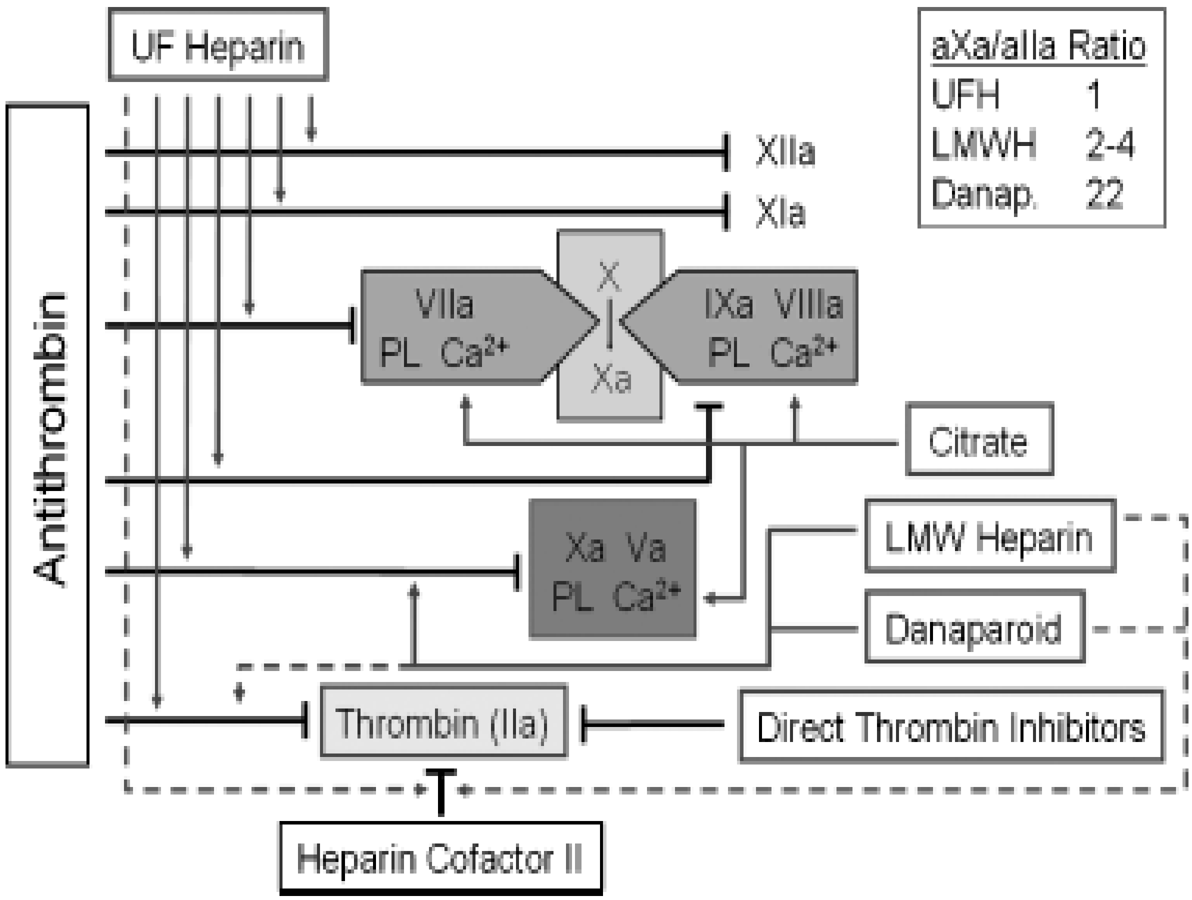
The intrinsic pathway of coagulation involves a sequence of reactions leading to fibrin formation, beginning with the contact activation of factor XII, and resulting in the activation of factor X to initiate the clotting cascade (Medical dictionary, 2011). The Extrinsic pathway leads to the formation of fibrin as the result of the release of tissue thromboplastin into the circulation. It is the mechanism that produces fibrin following tissue injury, beginning with formation of an activated complex between tissue factor and factor VII and leading to activation of factor X, inducing the reactions of the clotting cascade (Suranyi & Chow, 2010; Fischer 2007).

Appendix E. Cross Country Survey of Intradialytic Heparin (2011)

Program	Nursing Heparin dose adjustment policy	Physician	Clotting Scale	ACT	General Comments
Saint Paul Hospital, Saskatoon, Saskatchewan	No	Physician initiated with RN input	No Document appearance of dialyzer as heavily streaked etc. without assigning scores	No	-Nurses only ask for reassessment of orders if systems lost due to clotting or major clinical bleeding in patients -Lack of follow up in relation to heparin due to increase in patient acuity, decrease in number of experienced staff
Windsor Regional Renal Program, Ontario	Yes- RNs	Initial order and then nurses adjust based on policy	No Document post HD regarding visual appearance of dialyzer & venous chamber	No	-Do not have algorithm, start @500-1000units heparin and then titrate based on RN discretion
Dr. Georges- L. Dumont Regional Hospital Dialysis, Moncton New Brunswick	No	Physician initiated with RN input	No Nurses do not routinely document regarding dialyzer appearance, only document if system lost due to clotting	No	- Wide range of heparin dose variability based on different physician orders -Nurses only ask for reassessment of orders if systems lost due to clotting or major clinical bleeding in patients

Eastern Health, Newfoundland & Labrador	Yes- RNs/LPNs	Initial order and then nurses adjust based on policy	No Visual inspection assessment of clotting/fibrin formation	Yes	- Detailed protocol on heparin full intensity, heparin low intensity, heparin free dialysis based on ACT measurements, dialyzer appearance, & post hemastasis times
Humber River Regional, Ontario	No	Physician initiated with RN input	Yes Clear 1/3 clotted 2/3 clotted fully clotted	No	-Nurses only ask for reassessment of orders if systems lost due to clotting or major clinical bleeding in patients -large amount of heparin dose variability based on different physician
Thunder Bay Regional Health Sciences Centre	Medical heparin directives that can be implemented by RNs	Initial order and then RNs adjust based on medical directives	No Document regarding dialyzer and venous chamber streaking	Yes	Criteria & direction for over & under coagulation include changes to heparin dosage by 500units Medical directives for heparin regime (Routine, Tight, or Heparin free)
BC Renal Agency, British Columbia	Yes- RNs	Initial order by physician and then nurses adjust by 500U increments based on heparin algorithm	Yes 0-Clear 1-small clots/streaks 2- moderate clots/streaks 3- large clots/ streaks 4- completely clotted	No	-Aim for dialyzer clearance of 0-1 -Heparin algorithm directs nurses for heparin changes depended on when clotting timing of first or last part of run, or prolonged bleeding post HD
Southern Alberta Renal Program, AB	Yes- RNs & LPNs	Initial order and then nurses adjust based on policy/algorithm	Yes 0-Clear 1-few strands/small clots 2- ½ clotted 3- ¾ clotted 4-completely clotted	No	-Aim for dialyzer score of 1 -Nurses adjust heparin based on appearance of dialyzer and post needling clotting times Appendix C

Appendix F. Anticoagulant effect of UFH, LMWH, Danaparoid, Citrate, Direct thrombin inhibitors



Targets of selected anticoagulants within the clotting cascade (Fischer, 2007, p, 180)

According to Fisher (2007), ‘Antithrombin and heparin cofactor II inhibit key factors in the clotting cascade. Unfractionated heparin (UFH), low molecular-weight heparin (LMWH), and danaparoid are indirect agents increasing the activity of the natural inhibitors. Direct thrombin inhibitors block thrombin. Citrate chelates calcium and thereby inhibits all steps of the coagulation cascade’ p.180.

Appendix G. Intradialytic Heparin Reduction Study Data Collection Form

Run-In Visit 1 Subject #:

Date: ______________ Time: ______________ Pt. Initials: _________ DOB: ______________

Wt: ________ kg (Prescribed Target Weight) Wt: ________ kg (Pre Dialysis) Wt: ________ kg (Post Dialysis)

HEPARIN PROTOCOL ASSESSMENT

- Baseline Boost: ________ units
- Hourly Rate: ________ units/Hr
- Time Off: ________ min

BP ASSESSMENT – Pre dialysis ❋Please note that BP assessment will be completed at the initiation of hemodialysis

BP after Supine/Sitting x 5 minutes @ _____:_____ hrs BP = _____ /_____ mmHG HR: _____ bpm

BP ASSESSMENT – Post dialysis

BP after Supine/Sitting x 5 minutes @ _____:_____ hrs BP = _____ /_____ mmHG HR: _____ bpm

FIBER BUNDLE VOLUME ASSESSMENT ❋Run-In Visit 2, Visit 5❋

Pre-Dialysis: QB Gambro _________ QB Transonic _________ FBV1 _________ FBV2 _________

Post-Dialysis: QB Gambro _________ QB Transonic _________ FBV1 _________ FBV2 _________

Dialyzer: see run sheet

WASHBACK VOLUME ASSESSMENT ❋Run-In Visit 3, Visit 6❋

Post-Dialysis: _________

REVIEW

Concomitant Medication changes yes ☐ no ☐ ❋ If yes, please update con med sheet

Adverse Events yes ☐ no ☐ ❋ If yes, please update AE sheet and report to site PI

Serious Adverse Events yes ☐ no ☐ ❋ If yes, please update SAE sheet and report to site PI

Dialyzer/Venous Chamber yes ☐ no ☐ ❋Complete Independent Staff Nurse Assessment Sheet

Hemodialysis Run Sheet yes ☐ no ☐ ❋ Print Hemodialysis Treatment Record

HEPARIN DOSE ASSESSMENT – Post dialysis

Dialyzer Photos: Tripod Distance = 40 cm Height = 80 cm Lighting corrected: YES - ☐ NO - ☐

Venous Chamber Photo: Tripod Distance = 20 cm Height = 90 cm Lighting corrected: YES - ☐ NO - ☐

Heparin dose adjustment guide – see APPENDIX 1: Intradialytic Heparin Protocol

Area Assessed	Clotting Scale Assessed	Heparin Dose Adjustment Required	PARIS Kardex updated	Photographs complete
Dialyzer		YES - ☐ NO - ☐	YES - ☐ NO - ☐ N/A - ☐	each at 90 ° ⇨ 1 - ☐ 2 - ☐ 3 - ☐ 4 - ☐
Venous Chamber		YES - ☐ NO - ☐	YES - ☐ NO - ☐ N/A - ☐	1 - ☐ YES - ☐ NO - ☐
Area Assessed	**Unusually Prolonged Bleeding**	**Heparin Dose Adjustment Required**	**PARIS Kardex updated**	**Heparin Algorithm Adjusted**
Access site post HD Site Hold Time: _____ min	YES – ☐ NO - ☐	YES - ☐ NO - ☐	YES - ☐ NO - ☐ N/A - ☐	Baseline Boost:________ units Hourly Rate: ________ units/Hr Time Off: ________ min

Appendix H. Additional Statistical Data

Cumulative heparin dosage: Repeated measure one way ANOVA
Tests of Within-Subjects Effects
Measure: MEASURE1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
run	Sphericity Assumed	41357530.702	5	8271506.140	6.812	.000
	Greenhouse-Geisser	41357530.702	3.425	12076832.933	6.812	.000
	Huynh-Feldt	41357530.702	4.327	9558300.537	6.812	.000
	Lower-bound	41357530.702	1.000	41357530.702	6.812	.018
Error(run)	Sphericity Assumed	109275885.965	90	1214176.511		
	Greenhouse-Geisser	109275885.965	61.642	1772761.408		
	Huynh-Feldt	109275885.965	77.884	1403065.391		
	Lower-bound	109275885.965	18.000	6070882.554		

5.8 Cumulative heparin dosage Pairwise T test Comparisons

Measure: MEASURE_1

(I) run		Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
1	2	1076.316*	169.121	.000	504.62	1648.006
	3	1497.368*	289.547	.001	518.595	2476.141
	4	1792.105*	334.871	.001	660.121	2924.089
	5	1698.947*	413.430	.010	301.404	3096.491
	6	1415.789*	386.865	.027	108.046	2723.533
2	1	-1076.316*	169.121	.000	-1648.006	-504.626
	3	421.053	290.450	1.000	-560.774	1402.880
	4	715.789	351.543	.851	-472.554	1904.133
	5	622.632	463.567	1.000	-944.394	2189.657
	6	339.474	379.531	1.000	-943.478	1622.425
3	1	-1497.368*	289.547	.001	-2476.141	-518.595
	2	-421.053	290.450	1.000	-1402.880	560.774
	4	294.737	226.139	1.000	-469.695	1059.168
	5	201.579	407.530	1.000	-1176.021	1579.179
	6	-81.579	361.875	1.000	-1304.847	1141.689
4	1	-1792.105*	334.871	.001	-2924.089	-660.121
	2	-715.789	351.543	.851	-1904.133	472.554
	3	-294.737	226.139	1.000	-1059.168	469.695
	5	-93.158	371.321	1.000	-1348.359	1162.043
	6	-376.316	343.706	1.000	-1538.168	785.536
5	1	-1698.947*	413.430	.010	-3096.491	-301.404
	2	-622.632	463.567	1.000	-2189.657	944.394
	3	-201.579	407.530	1.000	-1579.179	1176.021
	4	93.158	371.321	1.000	-1162.043	1348.359
	6	-283.158	448.202	1.000	-1798.244	1231.929
6	1	-1415.789*	386.865	.027	-2723.533	-108.046
	2	-339.474	379.531	1.000	-1622.425	943.478
	3	81.579	361.875	1.000	-1141.689	1304.847
	4	376.316	343.706	1.000	-785.536	1538.168
	5	283.158	448.202	1.000	-1231.929	1798.244

Based on estimated marginal means
* The mean difference is significant at the .05 level.
Adjustment for multiple comparisons: Bonferroni

5.9 KT/V table

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
run	Sphericity Assumed	.095	5	.019	1.671	.157
	Greenhouse-Geisser	.095	2.543	.037	1.671	.201
	Huynh-Feldt	.095	3.371	.028	1.671	.185
	Lower-bound	.095	1.000	.095	1.671	.223
Error(run)	Sphericity Assumed	.627	55	.011		
	Greenhouse-Geisser	.627	27.971	.022		
	Huynh-Feldt	.627	37.086	.017		
	Lower-bound	.627	11.000	.057		

5.9.1 Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ktv1	1.3376	17	.28680	.06956
	ktv2	1.3353	17	.29994	.07275
Pair 2	ktv1	1.3450	16	.29455	.07364
	ktv3	1.2975	16	.30715	.07679
Pair 3	ktv1	1.3707	14	.29206	.07806
	ktv4	1.3471	14	.27457	.07338
Pair 4	ktv1	1.3376	17	.28680	.06956
	ktv5	1.2147	17	.36009	.08733
Pair 5	ktv1	1.3481	16	.29283	.07321
	ktv6	1.3000	16	.32748	.08187

*KT/V 1=run 1, baseline; KT/V2=run2, start of heparin study protocol; KT/V3=run3; KT/V4=run4; KT/V5=run5; KT/V6=run6

5.9.2 Access site hold times

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
run	Sphericity Assumed	17.802	5	3.560	1.391	.238
	Greenhouse-Geisser	17.802	3.155	5.643	1.391	.257
	Huynh-Feldt	17.802	4.092	4.350	1.391	.247
	Lower-bound	17.802	1.000	17.802	1.391	.257
Error(run)	Sphericity Assumed	192.031	75	2.560		
	Greenhouse-Geisser	192.031	47.319	4.058		
	Huynh-Feldt	192.031	61.383	3.128		
	Lower-bound	192.031	15.000	12.802		

5.9.3 Access site hold times run 1-6 in minutes

Descriptive Statistics

	Mean	Std. Deviation	N
Access hold time run1	5.3750	1.89297	16
Access hold time run 2	6.1250	1.85742	16
Access hold time run 3	4.8750	1.36015	16
Access hold time run 4	5.0625	1.23659	16
Access hold time run 5	5.1250	1.62788	16
Access hold time run 6	5.7500	2.64575	16

5.9.4 Access hemostasis time Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	run1 - 2	-.75000	2.14476	.53619	-1.89286	.39286	-1.399	15	.182
Pair 2	run1 - 3	.50000	1.50555	.37639	-.30225	1.30225	1.328	15	.204
Pair 3	run1 - 4	.31250	1.88746	.47186	-.69326	1.31826	.662	15	.518
Pair 4	run1 - 6	-.37500	2.72947	.68237	-1.82943	1.07943	-.550	15	.591

5.9.5 FBV pre run 2-pre run 5 difference

FBV_diff_2

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	-24.53	1	5.3	5.6	5.6
	-6.47	1	5.3	5.6	11.1
	-6.04	1	5.3	5.6	16.7
	-5.79	1	5.3	5.6	22.2
	-3.17	1	5.3	5.6	27.8
	.00	1	5.3	5.6	33.3
	.90	1	5.3	5.6	38.9
	1.69	1	5.3	5.6	44.4
	3.15	1	5.3	5.6	50.0
	5.38	1	5.3	5.6	55.6
	5.74	1	5.3	5.6	61.1
	5.92	1	5.3	5.6	66.7
	6.04	1	5.3	5.6	72.2
	7.29	1	5.3	5.6	77.8
	7.94	1	5.3	5.6	83.3
	8.57	1	5.3	5.6	88.9
	11.25	1	5.3	5.6	94.4
	13.74	1	5.3	5.6	100.0
	Total	18	94.7	100.0	

5.9.6 FBV_diff_5

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	-73.57	1	5.3	5.6	5.6
	-28.95	1	5.3	5.6	11.1
	-14.11	1	5.3	5.6	16.7
	-13.39	1	5.3	5.6	22.2
	-9.28	1	5.3	5.6	27.8
	-8.78	1	5.3	5.6	33.3
	-5.79	1	5.3	5.6	38.9
	-2.29	1	5.3	5.6	44.4
	.76	1	5.3	5.6	50.0
	2.61	1	5.3	5.6	55.6
	3.45	1	5.3	5.6	61.1
	3.48	1	5.3	5.6	66.7
	4.76	1	5.3	5.6	72.2
	5.30	1	5.3	5.6	77.8
	6.82	1	5.3	5.6	83.3
	8.03	1	5.3	5.6	88.9
	9.43	1	5.3	5.6	94.4
	19.05	1	5.3	5.6	100.0
	Total	18	94.7	100.0	
Missing	System	1	5.3		

5.9.7 Assessor for dialyzer clotting scale Wilcoxon test

Test Statistics

	sn2 - sn1	hd - sn1	cne - sn1
Z	-.816[b]	-2.183[b]	-2.673[b]
Asymp. Sig. (2-tailed)	.414	.029	.008
Exact Sig. (2-tailed)	.688	.049	.013
Exact Sig. (1-tailed)	.344	.025	.006
Point Probability	.234	.018	.006

a. Wilcoxon Signed Ranks Test

b. Based on positive ranks.

5.9.8 Assessor for dialyzer clotting scale Friedman Test

Ranks

	Mean Rank
sn1	2.72
sn2	2.64
hd	2.34
cne	2.30

Test Statistics[a]

N	48
Chi-Square	10.807
df	3
Asymp. Sig.	.013
Exact Sig.	.013
Point Probability	.003

a. Friedman Test

*sn1=study nurse score 1; sn2=study nurse score 2; hdn=hemodialysis nurse; cne=clinical nurse educator

Appendix I. Citrasate Study Photo Blinding Key

Blinded ID #	Subject Number	Date of Photos	Visit #
0001	MWF02	30-Jan-12	Run-In Visit 4
0002	MWF01	30-Jan-12	Run-In Visit 7
0003	MWF03	22-Feb-12	Run-In Visit 11
0004	MWF04	15-Feb-12	Run-In Visit 8
0005	MWF01	6-Feb-12	Run-In Visit 10
0006	MWF01	10-Feb-12	Run-In Visit 12
0007	MWF02	2-Mar-12	Run-In Visit 18
0008	MWF03	6-Feb-12	Run-In Visit 4
0009	MWF02	1-Feb-12	Run-In Visit 5
0010	MWF04	6-Feb-12	Run-In Visit 4
0011	MWF03	8-Feb-12	Run-In Visit 5
0012	MWF04	20-Feb-12	Run-In Visit 10
0013	MWF08	16-Apr-12	Run-In Visit 1
0014	MWF08	18-Apr-12	Run-In Visit 2
0015	MWF08	23-Apr-12	Run-In Visit 4
0016	MWF09	2-May-12	Run-In Visit 8
0017	MWF09	4-May-12	Run-In Visit 9
0018	MWF09	9-May-12	Run-In Visit 11
0019	MWF10	2-May-12	Run-In Visit 8
0020	MWF10	4-May-12	Run-In Visit 9
0021	MWF10	11-May-12	Run-In Visit 12
0022	MWF11	2-May-12	Run-In Visit 5
0023	MWF11	9-May-12	Run-In Visit 8
0024	MWF11	7-May-12	Run-In Visit 7
0025	MWF12	2-May-12	Run-In Visit 5
0026	MWF12	23-Apr-12	Run-In Visit 1
0027	MWF12	25-Apr-12	Run-In Visit 2
0028	MWF13	2-May-12	Run-In Visit 5
0029	MWF13	4-May-12	Run-In Visit 6
0030	MWF13	30-Apr-12	Run-In Visit 4
0031	MWF14	27-Jun-12	Run-In Visit 2
0032	MWF14	9-Jul-12	Run-In Visit 7
0033	MWF14	11-Jul-12	Run-In Visit 8
0034	MWF15	9-Jul-12	Run-In Visit 7
0035	MWF15	11-Jul-12	Run-In Visit 8
0036	MWF15	25-Jun-12	Run-In Visit 1
0037	MWF16	9-Jul-12	Run-In Visit 7
0038	MWF16	11-Jul-12	Run-In Visit 8
0039	MWF16	25-Jun-12	Run-In Visit 1
0040	MWF17	9-Jul-12	Run-In Visit 7
0041	MWF17	16-Jul-12	Run-In Visit 10
0042	MWF17	18-Jul-12	Run-In Visit 11

0043	MWF18	9-Jul-12	Run-In Visit 7
0044	MWF18	25-Jun-12	Run-In Visit 1
0045	MWF18	23-Jul-12	Run-In Visit 13
0046	MWF19	27-Jun-12	Run-In Visit 2
0047	MWF19	29-Jun-12	Run-In Visit 3
0048	MWF19	9-Jul-12	Run-In Visit 7

Appendix J. Citrasate Study Forms

Included in this appendix are:

1. Conjoint Health Research Ethics Board approval
2. Conjoint Health Research Ethics Board amendment approval
3. The effect of citrate dialysate on intradialytic heparin dose in hemodialysis: A randomaized crossover study
4. Patient consent form
5. Inclusion/exclusion criteria
6. Study data collection form
7. Study screening schedule
8. Study baseline data form