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Publication Date
2013

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UNIVERSITY OF CALIFORNIA

Los Angeles

Analysis of Preoperative Factors for

Time-Independent and Time-Dependent Outcomes

A thesis submitted in partial satisfaction

of the requirements of the degree Master of Science

in Clinical Research

by

Daniel A. DeUgarte

2013

ABSTRACT OF THE THESIS

Analysis of Preoperative Factors Associated with

Time-Independent Practices and Time-Dependent Outcomes

by

Daniel A. DeUgarte

Master of Science in Clinical Research

University of California, Los Angeles, 2013

Professor Janet Sinsheimer

Preoperative factors can influence clinical practice and surgical outcomes. Awareness of these factors can facilitate the evaluation of risks and benefits of procedures, help counsel patients, and improve clinical guidelines. Statistical analysis must be tailored to the outcome of interest. In this thesis, two studies are used to illustrate the analysis of preoperative factors associated with the time-independent practice of blood transfusion administration and time-dependent complications of peritoneal dialysis.

The thesis of Daniel A. DeUgarte is approved.

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2013

TABLE OF CONTENTS

PREFACE

Acknowledgements

General Acknowledgements

The author would like to acknowledge He-Jing Wang for her assistance with the

supplemental statistical analysis.

Acknowledgments for Publication 1 (Chapter 2)

<u>Publication Reference</u>

Burke Z, Chen J, Conceicao C, Hoffman R, Miller L, Taela A, DeUgarte DA. Evaluation of Preoperative and Intraoperative RBC Transfusion Practices at Maputo Central Hospital, Mozambique. *Transfusion.* In press.

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Acknowledgments for Publication 2 (Chapter 3)

BODY OF TEXT

CHAPTER 1:

Introduction

Preoperative factors can influence clinical practice and surgical outcomes. Awareness

of these factors can facilitate the evaluation of risks and benefits of procedures, help

counsel patients, and improve clinical guidelines. Statistical analysis must be tailored to

the outcome of interest. In this thesis, two published studies are used to illustrate the

analysis of preoperative factors associated with the time-independent practice of blood

transfusion administration and time-dependent complications of peritoneal dialysis.

Logistic regression is utilized to evaluate predictors of preoperative and intraoperative

blood transfusions. The Cox proportional hazard model is utilized to evaluate predictors

of mortality and reoperation following insertion of peritoneal dialysis catheters. In the

supplemental statistical section, we determine the goodness of fit of the aforementioned

models.

CHAPTER 2:

Evaluation of Preoperative and Intraoperative RBC Transfusion Practices at Maputo Central Hospital, Mozambique

ABSTRACT

BACKGROUND: The purpose of this study was to evaluate preoperative and intraoperative blood transfusion practices in Hospital Central (Maputo, Mozambique) and estimate the number of potentially avoidable transfusions.

STUDY DESIGN AND METHODS: A retrospective cohort study was performed. Age, comorbidities, hemoglobin, the potential for blood loss, and units of packed red blood cell (RBC) transfusions were recorded. Preoperative transfusions were evaluated to determine whether they met criteria established by the Mozambican Ministry of Health as well as proposed guidelines based on more restrictive protocols. Avoidable blood transfusions were defined as those preoperative transfusions that were not indicated based on these guidelines. Multivariate logistic regression was used to identify factors that predicted transfusion.

RESULTS: Two-hundred and five patients (age range: 0.1 - 86 years) underwent surgery in the main operating room during the two-week study period. Overall, thirty-five (17%) patients received sixty-eight transfusions. Of these, thirty-six transfusions were given preoperatively and thirty-two were given intraoperatively. Thirty-six percent of preoperative transfusions were avoidable according to national guidelines. Ninety-two percent were avoidable using more restrictive guidelines. The primary predictors of

preoperative blood transfusion were lower hemoglobin (odds ratio 0.390 / 1 g/dl; p<

0.0001) and the potential for blood loss (odds ratio 3.73; p=0.0410).

CONCLUSIONS: Adherence to existing hemoglobin thresholds recommended by

national blood transfusion guidelines could significantly reduce the number of

transfusions and the association risk of transfusion-transmissible infections. Adoption of

more restrictive guidelines is recommended to further improve blood transfusion

utilization and further reduce the transmission risk of HIV and hepatitis.

INTRODUCTION

Blood-borne infectious diseases are a major cause of morbidity and mortality in Mozambique. According to the World Health Organization (WHO), the prevalence of HIV infection in adults in Mozambique was 12% in 2009[1] While the majority of new infections are caused by sexual transmission, blood transfusions in sub-Saharan Africa have been shown to carry a significant risk of HIV transmission.[2] It is estimated that 6,650 HIV infections, 28,600 HBV infections, and 16,600 HCV infections were caused by blood transfusion in sub-Saharan Africa in 2011.[2] In Mozambique, blood transfusion was identified as a significant risk factor for the transmission of non-vertical and non-sexual transmission of HIV in a cohort of pediatric patients at Maputo Central Hospital.[3]

The WHO Blood Transfusion Safety program was created in 1975 to address the potential risks associated with blood transfusions in developing health systems. An essential component of this program included the appropriate utilization of blood in clinical settings. In a 2006 report on the status of blood safety in the WHO Africa Region, Mozambique was shown to be one of the countries with the most risk factors for transfusion-transmissible infections.[4] While projects are underway to improve screening and blood donation practices, little is being done to address the clinical transfusion practices in this high-risk country. Researchers at Maputo Central Hospital investigated hospital-wide blood transfusion practice and blood usage and identified the surgical services as frequent users of blood transfusions.[5] As a result of this study, it was specifically recommended that the surgical services review their blood transfusion practices. Thus, we sought to characterize the utilization of red blood cell (RBC)

4

transfusions in the preoperative and intraoperative setting at Maputo Central Hospital in

order to guide future interventions aimed at improving blood transfusion practices and

reducing the associated risks of transfusion-transmitted HIV and hepatitis.

MATERIALS AND METHODS

Study Design

Approval was obtained from the UCLA Institutional Review Board as well as the Mozambican Ministry of Health Bioethics Committee. A retrospective analysis of all pediatric and adult patients scheduled for elective surgery during a two-week period from July 10 to July 23, 2012 in the main operating rooms of Maputo Central Hospital was performed. The following data were collected from patient charts: age, comorbidities, surgical procedure, surgical service, preoperative hemoglobin concentrations, documented American Society of Anesthesia physical status classification (ASA),[6] the number of cross-matched RBC units requested for surgery, the number of preoperative and intraoperative RBC units transfused, estimated blood loss, and volume of crystalloid and colloid administered. All surgical cases performed during the study period were included in statistical analysis. We also identified cases that were cancelled and determined whether cancellations were affected by transfusion-related factors. Specifically, we determined the percentage of cases cancelled because requested cross-matched blood was not available, preoperative hemoglobin was not obtained, or the hemoglobin concentration was less than 10 g/dL.

Patients undergoing procedures with the potential for significant intraoperative blood loss were defined as those for whom the WHO blood ordering schedules recommend preparation of cross-matched RBC units.[7] For procedures not listed by the WHO, Ministry of Health blood ordering schedules were utilized.[8]

Preoperative blood transfusions were defined as those RBC transfusions administered within two weeks of surgery or last surgical intervention. Intraoperative blood transfusions were defined as those initiated during the operation or in the recovery room. Postoperative transfusions initiated on the ward were not evaluated. Preoperative hemoglobin was defined as the last recorded hemoglobin prior to the operation. Pre-transfusion hemoglobin was defined as the last recorded hemoglobin prior to a preoperative RBC transfusion; in patients who did not receive a transfusion, preoperative hemoglobin was used for statistical analysis. In adults, the volume per unit of RBCs administered was generally at a dosage of 5cc/kg.   In pediatric patients, a unit was defined as 10cc/kg RBC.

Every preoperative RBC unit transfused was evaluated to determine whether it was indicated according to any of three different transfusion criteria: (1) national criteria for the use of preoperative blood transfusions as outlined by the Mozambican Ministry of Health (MOH) guidelines,[8] (2) semi-restrictive criteria, and (3) restrictive criteria. Semi-restrictive and restrictive transfusion criteria were based on recommendations from the WHO, American Society of Anesthesia (ASA), AABB, and other sources (Table 2-1).[7,9-12] Avoidable blood transfusions were defined as those preoperative transfusions that were not indicated based on these guidelines. It became apparent during the study that there was insufficient documentation of estimated blood loss and intraoperative clinical parameters to reliably determine whether intraoperative transfusions were indicated. Therefore, only preoperative transfusions were evaluated. In order to estimate the

number of RBC transfusions that could be avoided yearly, we annualized the number of

avoidable preoperative transfusions observed over the two-week period.

Statistical Analysis

Spearman's correlation was used to evaluate the correlation between the number of

cross-matched units of RBCs recommended by the WHO guidelines and the number

requested by the surgical team for the procedure. Wilcoxon rank-sum test and Fisher's

exact test were utilized to compare characteristics between patients who received

transfusions and those that did not. Multivariate logistic backward stepwise regression

was utilized to identify factors that significantly predicted whether a patient received at

least one blood transfusion. A classification tree (CART) analysis was used to identify a

preoperative hemoglobin threshold that best predicted preoperative transfusion. JMP

10.0.0 (SAS Institute; Cary, NC) statistical software was utilized. Significance was

defined as $p<0.05$.

RESULTS

Study Setting

There were 282 cases scheduled in the main operating room during the two-week period of evaluation. There were 77 cancellations (27%). The majority of cancellations were due to limitations in elective time (48%), supply shortages (e.g. clean linens) (27%), and other miscellaneous reasons (11%). However, 14% of cancellations were transfusion-related. Of these, 46% were cancelled because requested cross-matched blood was not available, 27% because a preoperative hemoglobin was not obtained, and 27% because of a hemoglobin concentration <10 g/dL. In order to avoid counting rescheduled patients more than once, only 205 patients (73%) who underwent operations were included in the analysis. Surgical cases at the main operating rooms were performed by the following specialties: orthopedic (31%), general (24%), pediatric (15%), urology (12%), otolaryngology (6%), neurosurgery (6%), maxillofacial (3%), and plastics (3%). Obstetrics, gynecology, ophthalmology, cardiothoracic, urgent, and after-hour cases were performed offsite and therefore not included in the study.

Patient Demographics

The median age of patients was 24 years (range: 0.1 to 86). Nearly all (99%) patients had a preoperative hemoglobin concentration recorded. The majority (94%) of patients with documented ASA Classification were Class I (normal healthy) or II (mild systemic disease). The remaining patients (6%) were Class III (severe systemic disease). No patients were ASA Class IV (severe systemic disease that is a constant threat to life) or

V (moribund and not expected to survive without an operation). Demographic data is summarized in Tables 2-2 and 2-3 by preoperative and intraoperative transfusions.

Transfusions

Overall, thirty-five (17%) patients were transfused with sixty-eight units during the preoperative and intraoperative periods. Nineteen patients (9%) received thirty-six RBC units during the preoperative period. The median hemoglobin for patients undergoing preoperative transfusion was 8.8 g/dL. During the intraoperative period, twenty-two patients (11%) received a total of thirty-two RBC units. Median preoperative hemoglobin for patients receiving an intraoperative transfusion was 10.7 g/dl. Only six (17%) patients were transfused during both preoperative and intraoperative periods.

Cross-matched Blood - Potential for Significant Intraoperative Blood Loss

A total of eighty-four units of cross-matched blood were requested to be made available in the operating room for fifty-eight patients (28%). According to WHO blood ordering schedules, a total of eighty-two cross-matched units were recommended for thirty-nine patients (19%) undergoing procedures with the potential for significant intraoperative blood loss. There was a significant correlation between the number of cross-matched units recommended by WHO blood ordering schedules and the number requested by physicians at the hospital (Spearman's correlation coefficient 0.48; p<0.001).

Avoidable Preoperative Transfusions (Table 2-4)

Comparison of current practices with national guidelines demonstrated that eight

patients (42%) received a total of thirteen (36%) RBC units that were not indicated

during the preoperative period. Using semi-restrictive and restrictive transfusion criteria,

fifteen (79%) and eighteen (95%) patients respectively received at least one avoidable

transfusion (Table 2-5). Based on these results, the estimated number of preoperative

transfusions that could be avoided annually by adherence to national guidelines is 338

RBC units. Furthermore, adoption and adherence to either semi-restrictive or restrictive

guidelines could lead to the avoidance of the preoperative transfusion of 702 or 858

RBC units, respectively, each year.

Predictors of Preoperative Transfusion

Factors found to be significantly different between patients who received preoperative

transfusion and those who did not were hemoglobin concentration, ASA classification,

and potential for significant blood loss (Table 2-2). In multivariate analysis, lower

hemoglobin and potential for significant blood loss were significant predictors of

preoperative transfusion (Table 2-5). A hemoglobin threshold of <10 g/dl best predicted

preoperative transfusions using classification tree analysis.

Predictors of Intraoperative Transfusions

Preoperative factors found to be significantly different between patients who received an

intraoperative transfusion and those who did not were the potential for significant blood

loss, age, and ASA classification (Table 2-3).   In multivariate analysis, potential for

significant blood loss, older age, and lower hemoglobin were predictive of intraoperative transfusions (Table 2-5).

Of those patients who received an intraoperative blood transfusion, documentation for estimated blood loss was present in only 32%. Of these, the median estimated blood loss was 580 mL (range: 100 to 1500). The volume of crystalloid and/or colloid was recorded in 82% of patients with a median of 2.5 L (range: 0.25 to 11). No hemoglobin values were obtained or documented in the operating room or recovery room.

DISCUSSION

It is estimated that thousands of HIV, HBV, and HCV infections are caused by blood transfusions in sub-Saharan Africa annually.[2] Blood transfusion has been identified as an independent risk factor for HIV infection in Maputo Central Hospital.[3] In order to reduce the risk of transfusion-transmissible infections in countries with high HIV prevalence, it has been proposed that the use of transfusions should be limited to their "indispensible indications."[11,13,14] However, blood products are often over utilized in sub-Saharan Africa,[14,15] an observation that is supported by our study. We found that adherence to existing national guidelines could avoid more than one third of blood transfusions administered preoperatively, and that adoption of more stringent restrictive guidelines could avoid nearly all preoperative transfusions.

The number of avoidable transfusions is particularly alarming in the setting of a country with a high prevalence of HIV and other blood-borne diseases. Based on mathematical models, 7 (range 2 to 17) transmissions of HIV, 7 (range 2 to 15) transmissions of HBV, and 4 (range 1 to 8) transmissions of HCV are estimated per 1000 blood transfusions in Mozambique [courtesy of Sudha Jaramayan].[2] Using these estimates, adherence to current national guidelines could prevent transmission of two HIV infections annually in the study setting alone. Adoption of restrictive guidelines could avoid an estimated six HIV infections per year. These estimates apply only to the preoperative period in the study setting described. When these findings are extrapolated to the intraoperative and postoperative periods, all services at Maputo Central Hospital, and across the entire

country, the number of avoidable transfusions and associated transfusion-transmissible infections is likely substantial.

Adoption of restrictive guidelines could also avoid noninfectious risks of blood transfusions including transfusions reactions and immunosuppression. Perioperative blood transfusions are associated with a higher adjusted risk of death, wound problems, and other complications.[16] The risks of blood transfusion are likely higher in low-income countries like Mozambique, where non-leukocyte depleted blood is utilized.[17]

Our study demonstrated that the primary predictor of preoperative transfusions at Hospital Central was a hemoglobin less than 10 g/dl. Mounting evidence supports lowering the hemoglobin threshold for preoperative blood transfusions.[16,18-21] The WHO Clinical Use of Blood Handbook states that "there is rarely a justification for the use of preoperative blood transfusion simply to facilitate elective surgery."[7] Restrictive transfusion thresholds with significantly lower hemoglobin concentrations can be used without compromising outcomes.[12,18,22,23] In fact, several studies have shown that restrictive hemoglobin thresholds (e.g. < 7 g/dL) are not only safe but may result in improved outcomes when compared to liberal thresholds (e.g. < 10 g/dL).[18,22,24]

The potential for significant blood loss was found to be a predictor of both preoperative and intraoperative transfusions. The number of cross-matched RBC units requested for procedures at Maputo Central Hospital correlated positively with, and in most cases exceeded, those recommended by WHO blood ordering schedules. This suggests that

physicians may be over-ordering cross-matched units in order to assure availability in the operating room. Further supporting this theory, several cases were cancelled due to lack of cross-matched blood. In order to avoid preoperative transfusions intended solely to accommodate potential blood loss, a reliable blood supply in the operating room is required to reassure physicians that it is safe to delay transfusions until clinically-significant intraoperative blood loss is confirmed. In practice, reductions in the utilization of preoperative transfusions could help to conserve cross-matched blood and improve availability for intraoperative use.

Our study found that intraoperative transfusions had insufficient documentation of estimated blood loss and intraoperative clinical parameters to reliably determine whether transfusions were indicated. In order to help guide decisions about intraoperative transfusions, more accurate estimations of blood loss and assessment of hemoglobin are necessary. Several strategies can be employed: 1) implement gravimetric and lap sponge techniques to better estimate blood loss, 2) train anesthesiologists to evaluate for clinical signs of poor perfusion, and 3) introduce hemoglobin analyzers that provide rapid results.[25] Quality improvement projects mandating recording of intraoperative data could aid with monitoring of intraoperative transfusion practices.

Our study is limited by the retrospective design and the short duration of data collection. It is conceivable that annual estimates based on the study period may not accurately reflect seasonal variations in malaria and trauma that might impact preoperative

hemoglobin concentrations. However, in order to avoid the potential confounder of patients with active bleeding from trauma for whom hemoglobin values may not accurately represent perfusion status and need for blood transfusion, we limited our study to the main operating rooms where primarily elective cases are performed. Similarly, we did not evaluate whether intraoperative transfusions were avoidable because the data was insufficient. Thus, our estimates of avoidable transfusions are likely low.

In summary, a large number of preoperative blood transfusions at Maputo Central Hospital could potentially be avoided. It has been shown that introduction of blood transfusion guidelines in the surgical setting can effectively reduce the number of unnecessary transfusions.[26,27] In addition to reducing the risk of transfusion-transmitted infections, decreasing the number of unnecessary transfusions could decrease associated costs and preserve the limited blood supply. In the future, several steps must be employed to improve transfusion practice and reduce the number of unnecessary transfusions: 1) lower hemoglobin thresholds and promote the utilization of clinical indicators of poor perfusion (e.g. pallor, delayed capillary refill, tachycardia, and decreased urine output) to guide decision-making about blood transfusions, 2) improve availability and reliability of cross-matched blood, 3) improve methods of estimating and recording intraoperative blood loss, and 4) establish a blood transfusion committee to update local guidelines and routinely audit transfusion practices.[14]

Table 2-1 – Preoperative RBC Transfusion Criteria Utilized for Analysis

Preoperative RBC Transfusion Criteria Utilized for Analysis. National guidelines were obtained from the Mozambican Ministry of Health. Restrictive and semi-restrictive criteria were adapted from several sources including World Health Organization (WHO), American Society of Anesthesia, and AABB.

Criteria	Absolute hemoglobin indication	Additional hemoglobin indications
National[8]	< 8 g/dL	< 10 g/dL in children up to age 13 when alternative therapy does not improve anemia sufficiently < 10 g/dL in patients with severe respiratory insufficiency or unstable coronary artery disease
Semi-restrictive[7,9]	< 7 g/dL	< 7 g/dL in hospitalized stable adults and children with little/no expected blood loss < 8 g/dL in hospitalized stable adults and children with 1 unit suggested on WHO blood ordering schedule < 9 g/dL in hospitalized stable adults and children with 2+ units suggested on WHO blood ordering schedule
Restrictive[10-12]	< 6 g/dL	< 8 g/dL in patients with evidence of myocardial ischemia, recent stroke, age>80, evidence of ongoing organ ischemia, or the actual or potential presence of ongoing bleeding

Table 2-2 – Preoperative Transfusion Baseline Demographics

Characteristics of patients who underwent preoperative RBC transfusions within 2 weeks of surgery. Values are represented as either median (range) or number (%). Potential Significant Blood Loss was determined based on WHO blood ordering schedules. ASA – American Society of Anesthesia physical status classification. p-values were obtained using Wilcoxon rank-sum or Fisher's exact test.

	Not transfused	Transfused	Total	p-value
Patients (#)	186	19	205	
Median Age in Years (range)	25 (0.1-86)	20 (0.5-65)	24 (0.1-86)	0.557
Median Hg in g/dL (range)	11.9 (7.6-18.3)	8.8 (6.1-15.7)	11.8 (6.1-18.3)	<0.0001
Potential Significant Blood Loss				0.013
Yes	31 (17%)	8 (42%)	39	
No	155 (83%)	11 (58%)	166	
ASA				0.0055
I	93 (50%)	3 (16%)	96	
II	72 (39%)	11 (58%)	83	
III	8 (4%)	3 (16%)	11	
Not Recorded	13 (7%)	2 (10%)	15	
Number of Cases by Service (%)				0.87
Orthopedic	59 (32%)	5 (26%)	64	
General	43 (23%)	5 (26%)	48	
Pediatric	28 (15%)	2 (11%)	30	
Other	56 (30%)	7 (37%)	63	

Table 2-3 - Intraoperative Transfusion Baseline Demographics

Characteristics of patients who underwent intraoperative packed red blood cell transfusions. Values are represented as either median (range) or number (%). Potential Significant Blood Loss was determined based on WHO blood ordering schedules. ASA – American Society of Anesthesia physical status classification. p-values were obtained using Wilcoxon rank-sum or Fisher's exact test.

	Not transfused	Transfused	Total	p-value
Patients (#)	183	22	205	
Median Age in Years (range)	22 (0.1-86)	39 (4-78)	24 (0.1-86)	0.0005
Median Hg in g/dL (range)	11.9 (7.6-18.3)	10.7 (8.3-17.1)	11.8 (6.1-18.3)	0.0807
Potential Significant Blood Loss				<0.0001
Yes	24 (13%)	15 (68%)	39	
No	159 (87%)	7 (32%)	166	
ASA				0.0054
I	92 (50%)	4 (18%)	96	
II	69 (38%)	14 (64%)	83	
III	8 (4%)	3 (14%)	11	
Not Recorded	14 (8%)	1 (4%)	15	
Number of Cases by Service (%)				0.096
Orthopedic	55 (30%)	9 (41%)	64	
General	46 (25%)	2 (9%)	48	
Pediatric	29 (16%)	1 (5%)	30	
Other	53 (29%)	10 (45%)	63	

Table 2-4. Avoidable Preoperative Transfusions

Each RBC unit transfused preoperatively was classified as indicated or avoidable based on criteria defined in Table 2-1. The number and percentage of patients that received avoidable transfusions was also determined.

	National	**Semi-Restrictive**	**Restrictive**
Number of RBC Units (%)			
Indicated	23 (64%)	9 (25%)	3 (8%)
Avoidable	13 (36%)	27 (75%)	33 (92%)
Number of Patients (%)			
All Transfusions Indicated	11 (56%)	4 (21%)	1 (5%)
≥ 1 Avoidable Transfusion	8 (42%)	15 (79%)	18 (95%)

Table 2-5 – Results of Multivariate Analysis

Results of multivariate logistic regression to identify predictors of transfusion. Odds ratios for hemoglobin are calculated for every 1g/dl increase in hemoglobin concentration.   Odds ratios for age are calculated for every 1-year increase in age.

Predictors of Preoperative Transfusion

	Odds Ratio	95% CI	p-value
Hemoglobin	0.39	0.25-0.55	<0.0001
Potential Blood Loss	3.73	1.06-13.2	0.041

Predictors of Intraoperative Transfusion

	Odds Ratio	95% CI	p-value
Potential for Significant Blood Loss	10.7	3.73-33.8	<0.0001
Age	1.03	1.01-1.06	0.016
Preoperative Hemoglobin	0.697	0.50-0.41	0.018

CHAPTER 3:

Risk Factors for Morbidity and Mortality in Pediatric Patients with Peritoneal Dialysis Catheters

ABSTRACT

Purpose: As peritoneal dialysis (PD) is the preferred long-term dialysis modality in the pediatric population, we sought to identify risk factors for mortality and reoperation.

Methods: A retrospective review of patients undergoing PD catheter insertions at a single center from 1994-2009 was performed. The following variables were evaluated: age (<1 year), comorbidities, omentectomy, concomitant gastrostomy, and laparoscopic technique. Multivariable Cox regressions analyses were used to evaluate patient survival and reoperation-free survival of PD catheters.

Results: 207 patients with a median age of 10 years underwent PD insertion. Mortality was 7% with a median follow up of 72 months. Reoperation for malfunction and infection was required in 49% of patients with a median PD catheter survival of 11 months. Reoperation for hernias occurred in 14% of patients. Multivariate Cox regressions analyses identified age <1 year, lack of omentectomy, concomitant gastrostomy, and prematurity as variables significantly associated with higher rates of mortality or reoperation.

Conclusions: In this large study of pediatric patients undergoing PD, higher complications rates were noted in infants less than one year of age. Concomitant gastrostomy was associated with a higher rate of reoperation for infection. Failure to perform omentectomy was associated with a higher rate of catheter failure.

INTRODUCTION

Peritoneal dialysis (PD) is currently the therapy of choice to bridge pediatric patients

with end-stage renal disease to transplant. Although catheter quality and surgical

technique have improved, the reported incidence of complications remains high in

infants less than one year of age.[28,29] Successful insertion of the PD catheter remains

challenging in this age group due to the large catheter size relative to the infant's thin

and fragile abdominal wall.[30] In addition, rapid changes in body mass and length within

the first four years of life, along with increases in intraperitoneal pressure promote the

risk of hernia and leakage.[30] Exit site infections and peritonitis remain the most common

causes of treatment failure in children ages one to seven with 25% of younger patients

experiencing complications within the first six months following surgery.[31] In addition to

the risk of infection, poor catheter survival has been documented in the pediatric

population.[32]

Despite the increased rate of complications, there is limited data regarding specific risk

factors that predispose patients to catheter-related morbidity and mortality, especially in

the infant population. To identify such variables, we performed a retrospective analysis

of patients undergoing peritoneal dialysis catheter implantation at a single institution

over a 15-year period (1994-2009). We hypothesized that infants under one year of age

are at increased risk of death and reoperation.

METHODS

We performed a retrospective chart review of all patients who had surgical peritoneal

dialysis catheter placement at Ronald Reagan Medical Center from 1994 to 2009.

Institutional review board approval was obtained prior to record retrieval (#10-001285).

We identified 214 patients who underwent at least one catheter insertion at our

institution. Four individuals were excluded from the study due to lack of follow up. Three

peritoneal dialysis catheter insertions were excluded because they were performed in

the intensive care unit on patients with renal failure who were too unstable for transport

to the operating room. Data was only collected for the first catheter insertion at our

institution to insure that all observations were independent. The technique for peritoneal

catheter insertion adhered to recommended guidelines [33]. All patients were routinely

given perioperative antibiotics covering gram-positive organisms. A total of nine

surgeons performed the procedures during the study period.

We evaluated the following outcomes: 1) mortality and 2) reoperation for infection,

malfunction, or hernia. Reoperation for infection was performed for cases of peritonitis

or exit site infection that failed medical therapy. Reoperation for catheter malfunction

was performed for cases of leakage or obstruction that did not resolve with conservative

measures. Reoperation for hernia was performed for any hernia (incisional, inguinal, or

umbilical) that required surgical repair. The following predictors were evaluated: age,

sex, prematurity, major congenital heart disease, pulmonary hypoplasia, history of prior

peritoneal dialysis catheter placement at an outside hospital, lack of omentectomy,

concomitant gastrostomy, and laparoscopic catheter insertion. Wilcoxon rank-sum test

and Fisher's exact test were used to compare groups.

Survival analysis was performed to account for differences in follow up period and time to resolution of renal failure (either spontaneous or due to renal transplantation). The analysis time for mortality was months until death or censorship at last follow up. For the other outcomes, analysis time was months until reoperation or first censored event (either death, renal transplantation, resolution of renal failure, noncompliance, or last follow up). Bivariate analysis using Cox proportional hazards models was utilized to identify risk factors that could be potentially significant predictors of each outcome ($p < 0.2$). The potential risk factors identified through bivariate analysis were then utilized in a multivariate Cox proportional hazards model. Backward stepwise regression was then performed with p-value <0.2 as a stopping rule. Significance was defined as p-value of <0.05.

RESULTS

A total of 207 patients underwent PD catheter insertion and were included in the analysis (Table 3-1). Median age was 12 years (range: 0-21). Median follow up was 72 months (range: 0-209). Median time to catheter removal was 11 months (0-103). Omentectomy was not performed in 52 (25%) patients. While were not able to routinely characterize the extent of omentectomy from operative reports, it became evident that three patients had undergone incomplete omentectomy as they developed omental plugging and required additional resection of the omentum. Seven (3%) patients had concurrent gastrostomy. The laparoscopic technique for catheter insertion was introduced towards the end of the study period and was performed on 19 (9%) patients with median age of 15 years (range: 0-21).

Death due to kidney failure, sequelae of premature birth, sepsis, or comorbid cardiac or pulmonary conditions occurred in 15 (7%) of the study population. Renal failure resolved spontaneously in 16 patients (8%). Eight-one patients (39%) were successfully bridged to renal transplantation. The majority (86%) of the patients that underwent renal transplantation did not require reoperation for catheter failure or hernia. Of the patients who required reoperation for infection, 78% had peritonitis and 22% had exit-site infections. Of the patients who required reoperation for malfunction, 34% had intra abdominal adhesions (11 omental, 4 were intestinal/mesenteric, 1 fallopian tube), 24% had a leak, 17% had fibrin plugs, 17% had symptomatic migration, and 8% were removed for other reasons (e.g. catheter fracture, dislodgement, peritoneal membrane failure). Noncompliance with peritoneal dialysis was an indication for catheter removal in 4% of patients.

Groups under and over 1 year of age were significantly different with respect to percentage of patients with prematurity, major congenital heart disease, pulmonary hypoplasia, and concomitant gastrostomy (Table 3-1). Patients less than one year of age had significantly higher mortality (24% vs. 4%), reoperation for leak (18% vs. 3%), and hernia requiring reoperation (33% vs. 10%). There were no significant differences in the type of hernia requiring reoperation between patients less than one year of age (5 ventral, 5 inguinal, 1 umbilical) and greater than one year of age (11 ventral, 6 inguinal, and 1 umbilical). Outcomes stratified by age are summarized in Table 3-1.

Mortality: A total of 15 deaths were observed during the study period, and the death rate was 0.09 deaths per 100 patient-months. Age less than one year, prematurity, lack of omentectomy, congenital heart disease, and pulmonary hypoplasia were identified as

potentially significant predictors on bivariate analysis. Only age less than one year and omentectomy were significant predictors in the final multivariate model (Table 3-2).

<u>Reoperation for Infection and Malfunction (Table 3-3)</u>: A total of 101 patients underwent reoperation for infection or malfunction. The hazard rate was 2.9 reoperations per 100 catheter-months. Age less than one year, concomitant gastrostomy, lack of omentectomy, prior peritoneal catheter dialysis catheter, and congenital heart disease were identified as potentially significant predictors on bivariate analysis. Only lack of omentectomy was identified as a significant predictor in the final multivariate model, and it was associated with nearly double the reoperative rate for infection and malfunction (Model 1). The reoperative rate for infection alone (n=55) was 1.6 reoperations per 100 catheter-months. Concomitant gastrostomy, age less than one year, and lack of omentectomy were identified as potentially significant predictors on bivariate analysis. Only concomitant gastrostomy and lack of omentectomy were significant predictors in the final multivariate model (Model 2). The reoperative rate for malfunction alone (n=46) was 1.3 reoperation per 100 catheter-months. Age less than one year and prior peritoneal dialysis catheter placement were identified as potentially significant predictors on bivariate analysis. On multivariate analysis, age less than one year was the only significant predictor for reoperation for malfunction (Model 3). Of the subset of patient who underwent reoperation for leak (n=11), age less than one year and prematurity were identified as potentially significant predictors on bivariate analysis. Age less than one year was the only significant predictor for catheter leakage requiring reoperation in the final multivariate model (Model 4).

Reoperation for Hernia (Table 3-4): The development of a hernia requiring operative repair was observed in 29 patients (14%). The reoperative rate for hernias was 0.8 per 100 catheter-months. Age less than one year, prematurity, and pulmonary hypoplasia were potentially significant predictors on bivariate analysis. Age less than one year and prematurity were the only significant predictors in the final multivariate model.

DISCUSSION

In this large series, we found that age less than one year was associated with significantly higher adjusted rates of mortality and higher rates of reoperation for leak and hernia. Furthermore, lack of omentectomy and concomitant gastrostomy were associated with higher rates of reoperation.

Several reasons may explain the higher rate of complications seen in infants less than one year of age. Anatomically, infants have thinner abdominal walls which may contribute to catheter leakage.[30] Other potentially contributing factors include poor nutritional status and a higher incidence of congenital renal hypoplasia/dysplasia and obstructive uropathy, congenital nephrotic syndrome, and polycystic kidney disease. Additionally, due to the complexity of obtaining vascular access in this age group, hemodialysis is rarely used. Therefore, the need for emergent peritoneal dialysis leads to a shorter interval of time before use and a rapid increase in fill volumes. Both these factors may contribute to a higher incidence of leak and hernia as observed in other studies.[34] Not surprisingly, we observed that prematurity was independently associated with higher rates of reoperation for hernias. However, prematurity was not found to be associated with higher rates of reoperation for other complications.

Omentectomy is thought to reduce the risk of adhesions and catheter occlusion and improve catheter survival.[35-37] While experimental data suggests that omentum may confer immunologic benefit,[38] our results suggest that failure to perform omentectomy is associated with a higher rate of reoperation for infection. Indeed, other centers have observed significantly lower rates of peritonitis in patients who undergo omentectomy.[35] It has been proposed that catheter malfunctions caused by omental plugging may lead

to increased catheter manipulation and secondarily increase the risk of infection.[35] Our analysis of omentectomy as a risk factor is limited by the lack of standardization with respect to indications for the procedure and technique. Some patients did not undergo omentectomy because the surgeon felt the omentum was foreshortened and unlikely to occlude the catheter. While some surgeons advocate for selective or partial omentectomy and/or omentopexy,[39] we identified a few patients who had undergone incomplete omentectomy and required additional resection of residual omentum that had occluded the catheter. It is still not clear to us why lack of omentectomy was associated with a trend toward higher rates of mortality. A selection bias may exist that favors avoiding omentectomy in patients less likely to survive. We attempted to address this concern by excluding patients who were unstable for transfer to the operating room and underwent insertion of the catheter in a critical care unit.

While gastrostomy can be an essential component of fluid and nutritional management in renal failure patients,[40] we found that concomitant gastrostomy was associated with an increased risk of reoperation for infection. Gastrostomy can increase the duration of a procedure and convert a clean operation to a clean-contaminated one. Furthermore, patients requiring gastrostomy may be malnourished, which could independently increase the risk of infection.[41] Other investigators have shown that gastrostomy insertion following peritoneal dialysis catheter insertion is associated with higher rates of fungal peritonitis and catheter failure.[34,42]

Many centers now advocate performing laparoscopic insertion of peritoneal dialysis catheters.[39,43] We did not observe any significant differences between the laparoscopic and open approaches with respect to the outcomes of mortality and reoperation for

malfunction or infection. However, the laparoscopic approach was performed in only 9% of patients in our study and primarily in older patients. Our ability to detect any differences may be influenced by the small sample size and confounders. Other centers have also failed to demonstrate any significant differences in outcomes using the laparoscopic approach.[36,44,45]

While significant improvements have been made in outcomes of pediatric patients with renal failure,[46] this study highlights several factors that are associated with PD catheter-related morbidity and mortality. In particular, physicians and caregivers should be aware that patients less than one year of age have higher rates of mortality and catheter leak and hernia requiring repair. Additionally concomitant gastrostomy may increase the risk infection. When gastrostomy is indicated, efforts to minimize contamination and place the tube away from the dialysis catheter exit site are advisable. Finally, while our results support the routine use of omentectomy and reinforce current recommended guidelines in the pediatric population,[28,33] randomized prospective trials are ultimately required to account for potential confounders and validate its role in preventing catheter-related complications.

Table 3-1 - Patient Demographics, Perioperative factors, and Outcomes

Data is presented as number of patients (%). Prior peritoneal dialysis (PD) catheter

refers to those patients who had a history of prior catheter placed at an outside hospital.

	Overall	< 1 yr	> 1 yr	p-value
	n= 207	n = 33	n = 174	
DEMOGRAPHICS				
Male sex	112 (58%)	19 (58%)	93 (53%)	0.707
History of Prematurity	24 (12%)	17 (52%)	7 (4%)	0.000
Congenital Heart Disease	9 (4%)	7 (21%)	2 (1%)	0.000
Pulmonary Hypoplasia	9 (4%)	9 (27%)	0 (0%)	0.000
Prior PD Catheter	37 (18%)	2 (6%)	35 (20%)	0.079
No Omentectomy	49 (24%)	10 (30%)	39 (22%)	0.372
Concomitant Gastrostomy	7 (3%)	5 (15%)	2 (1%)	0.001
Laparoscopic Insertion	19 (9%)	1 (3%)	18 (10%)	0.321
Median Follow Up (months)	72	42	76	<0.001
OUTCOMES				
Mortality	15 (7%)	8 (24%)	7 (4%)	0.001
Reoperation				
Infection or Malfunction	101 (49%)	19 (58%)	82 (47%)	0.343
Infection	55 (27%)	9 (27%)	46 (26%)	1.000
Malfunction	46 (22%)	10 (30%)	36 (21%)	0.254
Leak	11 (5%)	6 (18%)	5 (3%)	0.003
Hernia	29 (14%)	11 (33%)	18 (10%)	0.002

Table 3-2 - Multivariate Analysis for Mortality

Hazard ratios are presented for the final multivariate Cox regression model.

Mortality	Hazard Ratio	95% Confidence Interval	p-value
Age Less than One Year	7.85	2.82 – 21.81	0.000
No Omentectomy	2.79	1.01 – 7.71	0.048

Table 3-3 - Summary of Multivariate Models

Outcomes for reoperation by indication are listed. Wilcoxon rank-sum test was used to compare follow up period. Fisher's exact test was used to compare outcomes. Hazard ratios are presented for the final multivariate Cox regression models for each indication for reoperation.

Indication for Reoperation	Hazard Ratio	95% Confidence Interval	p-value
Model 1 - Infection + Malfunction			
Age Less than One Year	1.65	0.94 – 2.90	0.080
Concomitant Gastrostomy	2.20	0.83 – 5.88	0.114
No Omentectomy	1.86	1.15 – 3.01	0.012
Prior PD Catheter	0.56	0.31 – 1.03	0.062
Model 2 – Infection			
Concomitant Gastrostomy	5.01	1.51 – 16.61	0.008
No Omentectomy	1.92	1.07 – 3.43	0.028
Model 3 - Malfunction			
Age Less than One Year	2.19	1.07 – 4.45	0.031
Prior PD catheter	0.31	0.10 – 1.01	0.052
Model 4 - Leak			
Age Less than One Year	9.82	2.92 – 32.97	0.000

Table 3-4 - Reoperation for Hernia

Hazard ratios are presented for the final multivariate Cox regression models for reoperation for hernia.

	Hazard Ratio	95% Confidence Interval	p-value
Age Less than One Year	3.91	1.55 – 9.86	0.004
Prematurity	2.80	1.09 – 7.20	0.033

CHAPTER 4:

Supplemental Statistical Analysis

Overview

In this thesis, two studies were used to illustrate the analysis of preoperative factors

associated with the time-independent practice of blood transfusion administration and

time-dependent complications of peritoneal dialysis. Logistic regression was utilized to

evaluate predictors of preoperative and intraoperative blood transfusions. The Cox

proportional hazard model was utilized to evaluate predictors of mortality and

reoperation following insertion of peritoneal dialysis catheters. In the supplemental

statistical section, we determine the goodness of fit of the models utilized for statistical

analysis.

Multivariate models for preoperative predictors of transfusion.

Hosmer-Lemeshow goodness-of-fit test was utilized to evaluate the multivariate models

for preoperative predictors of preoperative and intraoperative blood transfusions (Table

2-5).

The model for preoperative blood transfusions demonstrated lack of fit (Chi-square

36.87, p<0.0001) when all patients were included. However, one patient outlier was

identified using influence diagnostics (Pearson residual 21.9, Deviance residual 3.51, CI

displacement C 1.49, Chi-square deletion difference 483, Deviance deletion difference

13.8).   When the outlier patient was removed, there was good fit observed (Chi-square

7.75, p=0.4581). Area under the receiver operating characteristic (ROC) curve

increased from 0.8985 to 0.9342 increased from when the outlier was excluded.

Exclusion of the outlier did not influence which predictors of preoperative transfusion

were identified by backward stepwise logistic regression although the effect of potential

blood loss is diminished.

	Outlier Included (Reported Results)		Outlier Excluded	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Hemoglobin	0.39 (0.25-0.55)	<0.0001	0.29 (0.17-0.45)	<0.0001
Potential Blood Loss	3.73 (1.06-13.2)	0.041	3.07 (0.74-12.7)	0.12

The chi-square for intraoperative blood transfusions demonstrated good fit (Chi-square

5.01, p=0.7561) when all patients were included. Area under the receiver operating

characteristic (ROC) curve was 0.8675.

Multivariate models for preoperative predictors of reoperation.

One way is to determine whether the proportional hazard assumption is violated is to

add a covariate-by-time interaction term into the proportional hazard model. If the

interaction term is significant, it should be included in the model or a stratified

proportional hazard model must be considered.

Schoenfeld residuals can be used to detect possible departure from the proportional

hazard assumption. Schoenfeld residuals should be independent of time. If there is an

association between Schoenfeld residuals and time, the covariate-by-time interaction term is evaluated as described above.

For all models of reoperation (Table 3-2, 3-3, and 3-4), covariates that potentially violated the proportional hazard assumption had non-significant covariate-by-time interaction terms.   Therefore, a stratified proportional hazard model was not utilized.

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