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The Relationship Between Central Venous Catheter and Post-Operative Complications in Patients Undergoing Hepatic Resection

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

by

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Abstract

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David C. O'Connor, Ph.D., DNAP, CRNA

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Hepatic resection is indicated for primary and secondary malignancies. Use of a low central venous pressure technique is associated with decreased blood loss in these cases. This technique has evolved; central venous catheters and high dose morphine are no longer used, and patients are extubated earlier. The purpose of this study is to assess a relationship between these changes and outcomes.

Central venous pressure has fallen out of favor as an accurate fluid measurement. Central venous catheters are associated with many complications. Outcomes in patients undergoing hepatic resection have improved over 20 years at one high volume institution.

Guided by Donabedian's theory of measuring outcomes, a non-randomized, non-experimental, retrospective, cohort design was conducted.

The independent variables were intraoperative insertion of a central venous catheter, use of morphine, and time of extubation. The dependent variables were

superficial and deep wound infections, number and severity of complications. The population sample is patients who submitted to partial hepatectomy at Memorial Sloan Kettering Cancer Center from 2007-2016.

Data was obtained from hepatobiliary and anesthesia databases at Memorial Sloan Kettering Cancer Center.

Data of 2518 from a possible 3903 patients were analyzed with chi square, univariate, Poisson and multivariate regressions. Univariate analysis for presence of CVC was significant for 90-day mortality (p 0.013). Use of morphine was significant for superficial wound infection (p 0.035), and a decrease in complications ($p <.001$). Amount of morphine was associated with fewer severe complications ($p <.001$). Incidental findings included a relationship between gender, total amount of fluids and number of segments resected.

The significance of CVC with 90-day mortality was eliminated with stepwise multivariate regression. The findings support the change in anesthetic practice with clinical significance. Incidental findings regarding fluids and segments are supported in the literature. Future research should include goal directed fluid therapy and investigation of the relationship between gender and outcomes.

Chapter 1: Introduction

Introduction

Each year in the United States, about 41,000 people are diagnosed with liver cancer, and nearly 29,000 die from the disease (Centers for Disease Control and Prevention, 2016). Liver resection is used to treat primary and secondary malignancies. However, there is a high-risk of hemorrhage during this procedure (Kingham et al., 2015). Large volumes of intraoperative blood loss are associated with significant morbidity (Cunningham et al., 1994)(Heriot & Karanjia, 2002). A safe and effective technique for minimizing blood loss was described by Cunningham et al. (1994) at Memorial Sloan Kettering Cancer Center (MSKCC) (Cunningham et al., 1994). The technique involved surgical control of blood inflow to the liver and anesthetic team management of fluids and venous capacity to influence blood backflow into the liver from the vena cava. From an anesthesia standpoint, this technique was called a low central venous pressure (LCVP) technique.

Background

LCVP anesthetic technique aided in minimizing blood loss during major liver resection (Melendez et al., 1998). The initial execution of the LCVP technique involved the surgical and anesthesia teams working in tandem. The surgeons controlled blood inflow to the liver with the Pringle technique, first described in 1908 by J.H. Pringle (Pringle, 1908). Until the specimen was removed and the patient was hemodynamically stable, the anesthesia team minimized fluids, maintained central venous pressure (CVP) at five mmHg or less and positioned the patient in the Trendelenburg (head down position). These maneuvers served to minimize the backflow of blood into the liver from the vena cava and venous sinuous network (Cunningham et al., 1994). Additionally, intravenous fentanyl, up to 500 mcgs, morphine, up to 50 mgs, and nitroglycerin 200 mcg boluses were administered to maintain the CVP at the hemodynamic target.

CVP monitoring was made possible with the insertion of a central venous catheter into the superior vena cava. First described in 1959 by Hughes and MacGovern, and later supported by Wilson et al. (1962), CVP was believed to be an accurate and reliable measurement of blood volume (Hughes & Magovern, 1959; Wilson, Grow, Demong, Prevedel, & Owens, 1962). Along with other fluid status indicators, such as heart rate and blood pressure, CVP was a critical tool in the development of the LCVP technique for liver resections at MSKCC (Cunningham et al., 1994; Melendez et al., 1998).

Systematic reviews by Marik, et al. (E. Marik P. & Cavallazzi, 2013; P. E. Marik, Baram, & Vahid, 2008) demonstrated a poor relationship between CVP and blood volume, resulting in questioning the veracity of its efficacy, and ultimately initiating a change in the LCVP technique in some settings. Adverse effects of introducing a central venous catheter (CVC) are well documented in the literature, and include pneumothorax, subclavian artery puncture, subclavian vein laceration, subclavian vein stenosis, hemothorax, thrombosis, air embolism, catheter misplacement, cardiac dysrhythmia, and site or systemic infection, all of which are associated with increased length of stay (Institute for Healthcare Improvement, 2012). This, combined with the evidence presented in the Marik publications (2008, 2009, 2013) showing low correlation between CVP and fluid status, led to a change in practice at MSKCC.

Since the Melendez et al. (1998) publication, the LCVP technique further evolved based on clinically derived evidence that supported change. The patients were no longer given high doses of morphine to lower the CVP in favor of sub lingual nitroglycerin, a potent vasodilator (Sand et al., 2014). This practice change led to patients who were more likely to be extubated at the end of the case. Shortly following this change, the papers by Marik et al. (2008, 2009, 2013) gained support and the practice of using CVCs in this patient population fell out of favor; fluid resuscitation no longer required management with central venous access due to decreased blood loss, and the idea that CVP was no longer considered a valid measurement of fluid status prevailed. Instead, patients undergoing partial hepatectomy were managed with two large bore peripheral intravenous lines and an arterial catheter for continuous blood pressure monitoring, in addition to standard monitors. At that time, dynamic monitoring was evolving into a reliable measurement of fluid status. Once the specimen was removed, and hemostasis attained, managing the fluids based on these parameters, in part based upon each patient's unique position on the Frank-Starling curve of fluid responsiveness, led to the final change in anesthetic technique. A primary outcome was that patients were receiving less intravenous fluid in the operating room.

Central venous access for partial hepatectomy was the standard of care at MSKCC until around 2010. The use of CVP monitoring and the LCVP anesthetic technique remains the standard of care at many other institutions where liver resections are performed. This project will provide a unique opportunity to assess the evolution of the LCVP anesthetic technique and its potential relationship with outcomes for patients undergoing partial hepatectomy.

Problem Statement

Evidence at MSKCC, a high-volume institution for the hepatic surgery, demonstrated a substantial decrease in morbidity and mortality rates after a partial hepatectomy for cancer between 1993 and 2012. Clinical researchers suggested this phenomenon was related to a decrease in number of major resections over time (Kingham, et al., 2015); however, one critical aspect of the procedure was not assessed, that is the associated simultaneous changes in anesthetic technique that occurred.

Purpose

The purpose of this project was to examine the data from MSKCC with an updated time frame (2007-2016) to assess whether there is a relationship between a change in anesthetic technique over time and selected outcomes. The utilization of an existing dataset will allow for a systematic study of changes in anesthetic technique that will inform best practice in the profession.

Research Questions and Objectives

The research question being addressed is as follows: Is there a relationship between intraoperative insertion of CVC for the purpose of fluid management in hepatic resection and outcomes? Examination of this question involved the assessment of two other milestones in the in the perioperative care of patients receiving the LCVP technique at MSKCC. The first was to examine the effect of a change in practice in the use of intraoperative morphine, and the second was to assess the relationship between extubation in the operating room (OR) and outcomes. The outcomes that were measured included complications associated with major organs, the gastrointestinal system as well as infection, hemorrhage, and wound breakdown. The objectives are to assess whether:

- There is a relationship between the insertion of intraoperative CVC and selected outcomes in patients undergoing hepatic resection.
- There is a relationship between the use of morphine for the purpose of lowering CVP for hepatic resection and selected outcomes.
- There is a relationship between extubation in the OR and outcomes in patients undergoing hepatic resection.

Assumptions

Historically, hepatic resection was associated with morbidity and mortality. Over time, with improved surgical techniques, alternative treatments, and improved patient selection, complications associated with this procedure have declined (Correa-Gallego et al., 2015; Kingham et al., 2015). There are other factors that may have had an effect on a change in outcomes for patients undergoing hepatic resection. Over the period of time being addressed (2007-2016), there was a change in environment; the operating rooms were upgraded, and several anesthetic medications once considered standard were eliminated from routine use, including droperidol, thiopental, pancuronium, and morphine. It should also be pointed out that although there was a hepatobiliary anesthesia team, individuals who administer anesthesia to patients undergoing hepatic resection at MSKCC have varying abilities and experience. The LCVP technique was expected to be used in these cases. However, individual practice and clinical judgment actions may have differed between anesthesia care providers.

For the purposes of the planned study, we assumed that the anesthesia care provided was equal on both operating room platforms and that a change in medications based on evidence and the conduct of individual anesthesia care providers had minimal impact on the outcomes being assessed.

Theoretical Framework

Avedis Donabedian described a framework for assessing the quality of care. Donabedian used structure, process, and outcomes in his theory measuring the quality of healthcare (Donabedian, 1978). The model that Donabedian proposed is widely accepted in evaluating the quality of health care (Harolds, 2015). For the purpose of this dissertation, the constructs may be considered to be hospital policy/practice (structure), whether a CVC was inserted, if patients were extubated in the OR, whether morphine was used, how the fluid status was managed (process) and incidence complications associated with major organs, the gastrointestinal system as well as infection, hemorrhage, wound breakdown and length of stay (outcome). Donabedian thought that process had specific importance in measuring quality. Additionally, Donabedian believed that focus should be on improving outcomes by way of improving process. However, not all improvements in structure and process significantly affect the outcome (Harolds, 2015).

Delineation and Justification of the Research Problem

The research problem is a gap in the literature describing the potential relationship between utilization of CVC for the purposes of managing fluid status for patients undergoing partial hepatectomy and outcomes. Use of CVP monitoring in this patient population has fallen out of favor at MSKCC. It was possible to look at the hepatobiliary database to assess change in outcomes by comparing cases pre and post this change in practice. It was also be possible to assess the relationship that other changes in the LCVP technique over the timeframe being investigated had with outcomes. The investigation looked specifically at three variables: use of morphine, insertion and use of CVC for CVP monitoring, and extubation in the OR and their relationship with the outcomes of patients who underwent partial hepatectomy at MSKCC between 2007 and 2016. This investigation is important because it sheds light on the potential influence on outcomes of an anesthetic technique as it evolved over nearly 20 years. Evidence-based practice is the integration of “the best available research evidence with information about patient preferences, clinician skill level, and available resources to make decisions about patient care” (American Association of Critical-Care Nurses., 1995). The results of the analysis will add to the knowledge base that was reported as a result of the Kingham et al. (2015), investigation. Additionally, the results will either support the change in practice or suggest that the there was no relationship between these changes and outcomes. It is unlikely that the LCVP technique in its current form is related to an increase in poor outcomes. However, this result should be considered. Ultimately, the findings will add to the literature that shapes anesthesia practice in this patient population as an important step in the ultimate goal of contributing to evidence-based practice.

Statement of Hypothesis

The primary hypothesis is that there is a relationship between presence of an intraoperative central venous catheter (CVC) placement and outcomes in patients who have undergone partial hepatectomy. Additional hypotheses include other changes to the LCVP technique and their relationship with outcomes: amount of time to extubation following the procedure, and the use of intraoperative morphine.

Scope of the Investigation

The project wass a non-randomized, non-experimental, retrospective, cohort design. Data was obtained from patient electronic records in the hospital database as reported by the health care team. Identifying cases was based on date of surgery and date billed for intraoperative CVC placement. Outcomes in the form of presence or absence of complication as described in the patient record are outlined in chapter 3 (Methods).

Retrospective cohort studies have many of the strengths of prospective cohort studies, and they have the advantage of being much less costly and time-consuming (Hully, Cummings, Brower, Grady, & Newman, 2013). Disadvantages of a retrospective study design include limited control of the investigator over the approach to sampling and follow-up population, and the nature and quality of the baseline measurements. The data may be incomplete, inaccurate, or measured in ways that are not ideal for answering the research question(s) (Hully et al., 2013). Challenges associated specifically with this project include those associated with retrospective research design;

consistency of measurements, other changes in practice, and missing data. The nature of the study should allow for efficient and economic acquisition of the needed data.

Overview of Remaining Chapters

This paper is divided into four remaining parts. Chapter two offers a comprehensive review of the literature regarding the use of CVP for the purposes of fluid management and the alternatives. Also included are alternative approaches to minimizing blood loss for patients undergoing partial hepatectomy. Donabedian's theory of evaluating the quality of medical care is also presented as it pertains to the proposed research. Chapter three provides methods and statistical analysis that will be utilized to answer the research questions. Chapter four includes a presentation of the study results. Finally, chapter five will deliver an interpretation and summary of the findings.

Chapter 2: Review of Literature

Background

Initially designed to test a technique that was described in animal studies, Hughes and Magovern (1959) studied 25 thoracic patients to test the efficacy of the measuring of the right atrial pressure in predicting changes in intravascular fluid volume (Hughes & Magovern, 1959). The authors concluded that measuring the right atrial pressure was an accurate and reliable method for assessing hemodynamics and suggested its use in any surgery where a change in hemodynamics may be anticipated (Hughes & Magovern, 1959).

Following the lead of Hughes and Magovern, Wilson and Grow (1962) described indications and a simplified technique to measure what they referred to as central venous pressure (Wilson et al., 1962). Their conclusions emphasized the importance of utilization of CVP as a trend and response to fluid therapy and not an isolated, static, or predetermined number (Wilson et al., 1962). Additionally, the authors described their first complication associated with accessing the vena cava for the purpose of measuring CVP, a fatal pulmonary embolism that developed as an embolus at the site of insertion, the saphenous vein. The technique was altered, accessing the superior vena cava via the antecubital fossa and then the subclavian vein. Following this change, the complications described were limited to superficial phlebitis and pneumothoraces (Wilson et al., 1962). The authors made no mention of systemic sepsis and encouraged the practice of monitoring CVP in this manner when indicated despite the reported complications. Other complications associated with, but not mentioned in this early study of insertion of central venous access include cardiac arrhythmia, pneumothorax, subclavian artery puncture, subclavian vein laceration, subclavian vein stenosis, hemothorax, thrombosis, air embolism, site infection, sepsis and catheter misplacement (Centers for Disease Control and Prevention., n.d.).

In 1994 Cunningham et al. published a paper in which they described an anesthetic technique utilizing the measurement of CVP to aid the surgeon in controlling intraoperative bleeding during partial hepatectomy. This LCVP technique, in addition to the surgeon’s control of hepatic inflow as first described in 1908 by J. H. Pringle as the Pringle technique (Huntington, Royall, & Schmidt, 2014), was reported as a safe and effective method that helped to decrease blood loss for these cases (Cunningham et al., 1994). The authors analyzed 36 retrospective and 64 prospective cases in which the LCVP technique was used during parenchymal resection. The technique involved maintaining CVP below five mmHg with fluid restriction, intravenous morphine and/or intravenous nitroglycerin with Trendelenberg position of the bed. The reported blood losses were considered acceptable for such procedures, and the authors concluded that the technique was effective (Cunningham et al., 1994).

A 1998 retrospective study conducted at Memorial Sloan Kettering Cancer Center by Melendez et al. reported that the LCVP technique during hepatic resection minimized blood loss and reduced mortality while preserving renal function (Melendez et al., 1998). Over an eight-year period, the authors analyzed data from 496 patients assessing outcomes and reported no intraoperative deaths, a median blood loss of 675 ml (range 40 ml-9000 ml) and an intraoperative transfusion rate of 33%. The incidence of renal dysfunction was 10%, and when compared to the previously reported 13% during standard care, it appeared as if there was an improvement with the utilization of the LCVP technique (Edwards & Blumgart, 1987). Presence of a central venous catheter not only allowed for the measurement of CVP, but it also afforded the anesthesia care provider the ability to rapidly infuse fluids should the need arise (Melendez et al., 1998). Finally, the authors underscored the necessity of the surgical and anesthesia teams working in tandem to facilitate the operative control of, and appropriate response to, hemorrhage (Melendez et al., 1998).

The goal of decreasing blood loss in the hepatic resection patient population is desirable because blood transfusion has been associated with poor outcomes (Cunningham et al., 1994; Gruttadauria et al., 2011; Melendez et al., 1998; Stephenson et al., 1988). One study in, particular, looked at patients with metastatic colorectal cancer. Stephenson et al. analyzed data from 55 patients with metastatic colorectal cancer who underwent surgical resection of liver disease. They reported that patients who received more than 11 units of red blood cells had a significantly decreased disease-free survival rate than those that received less than10 units of blood (Stephenson et al., 1988). In 2011, Gruttadauria et al. examined 90-day outcomes for patients who underwent liver resection for malignancy. The authors looked at 127 cases between 1999 and 2010 and found an association between intra-operative blood transfusion and outcomes. Patients who received transfusions had longer lengths of stay and higher complication rates than those who did not.

Current Research

Central venous pressure monitoring.

Since the inception of using CVP measurement for the purpose of predicting fluid status, researchers and practitioners have been encouraged to incorporate the reading into their clinical judgment. In 2007 Magder et al., published findings from 83 intensive care unit patients encouraging practitioners to utilize cardiac output measurements along with CVP to estimate fluid responsiveness based on the Frank-Starling curve (Magder & Bafaqeeh, 2007).

The most compelling evidence contrary to the practice of measuring CVP to predict fluid status comes from Marik et al. (Marik, Baram, & Vahid, 2008; Marik, Cavallazzi, Vasu, & Hirani, 2009; Marik P. & Cavallazzi R., 2013). In 2008, Marik et al. reviewed 24 studies and reported that there was no correlation between CVP and blood volume. Additionally, the findings failed to find a relationship between CVP and fluid responsiveness based on the Frank-Starling Curve (Marik et al., 2008). In 2009, Marik et al. conducted a meta-analysis of 29 studies which included a total of 685 patients. The purpose of the analysis was to determine the accuracy of dynamic measurements, stroke volume variation (SVV), pulse pressure variation (PPV) and systolic pressure variation (SPV). Additionally, the authors compared these dynamic measurements to that of the static CVP measurement. The authors reported that the dynamic measurements accurately, and consistently predicted fluid status. That is, with the use of fluid challenges, these measures predicted increase in stroke volume (SV) and therefore, cardiac output (CO) in patients being mechanically ventilated (Marik et al., 2009). The authors also reported that the dynamic measurements were significantly more accurate than any other variable reported to date as a predictor of fluid status including CVP, left ventricular end-diastolic area index (LVEDAI) measured by echocardiography and global end-diastolic volume index (GEDVI) as determined by transpulmonary thermodilution (Marik et al., 2009).

In 2013 Marik et al., updated their meta-analysis exploring the accuracy of using CVP as a measurement for fluid management (Marik P. & Cavallazzi R., 2013). The authors reviewed 43 studies that included a healthy control, 22 ICU and 20 surgical settings. The aim of the updated analysis was to incorporate recent studies into their previous (2013) findings. The authors stated that despite the rising evidence suggesting that CVP is an inaccurate measurement of fluid status, CVP remained a popular tool. The findings suggested that there “are no data to support the widespread practice of using central venous pressure to guide fluid therapy,” with the authors arguing that the traditional CVP approach should be abandoned (Marik P. & Cavallazzi R., 2013).

Contrary to the Marik et al. publications, CVP continues to appear in publications as a useful tool for measuring fluid status see. A 2010 publication, Scales et al. (2010) describe the rationale for, process of setting up and interpreting CVP monitoring for the purpose of continuing education. The authors point out several clinical situations in which CVP monitoring is appropriate including fluid resuscitation in major trauma, cardiac surgery, thoracic surgery, major abdominal surgery, to optimize fluid replacement in acute renal failure, to optimize fluid replacement in sepsis and to guide fluid replacement in heart failure (Scales, 2010). Referring to Magder’s 2007 publication, Scales supports the measurement of CVP for the previously mentioned purposes. This, despite Magder's main point that CVP should be used along with other measurements such as cardiac output and stroke volume as well as clinical judgment (Magder & Bafaqeeh, 2007).

Alternative trends in fluid status management.

Dynamic fluid measurements are those measurements that utilize circulatory variability during respiration to predict fluid status (Table 1).

Table 1. *Dynamic Measurements Defined*

Dynamic Measurement	Abbreviation	Manner of Measurement
Stroke Volume Variation	SVV	Arterial waveform SVmax - SVmin / SV mean
Systolic Pressure Variation	SPV	Arterial Waveform SBPmax - SBPmin
Pulse Pressure Variation	PPV	Arterial waveform SVmax - SVmin / SV mean
Pleth Variability Index	PVI	Sp02 waveform PPmax−PPmin)/[(PPmax+PPmin)/2

Note: ("White Paper: Stroke Volume Variation," n.d.)(Frédéric Michard, 2005)(Cannesson et al., 2008).

Dynamic fluid measurements have gained support of late due to improved technology and evidence that these measurements are accurate and consistent indicators of fluid status (Marik et al., 2009). These measurements use the changes in arterial and/or oxygen saturation waveform during mechanical, positive pressure, ventilation to predict where a patient lies on the Frank-Starling Curve of fluid responsiveness (Figure 1).

Accuracy and consistency were not always the case with dynamic measurements. In 2007 dynamic fluid measurements began to be more thoroughly vetted. As a result, critiques of these measurements were present in publications and editorials. At the time, their accuracy and consistency were variable, with error ranks reported to be above 30% (Frédéric Michard, 2007). This percentage was deemed

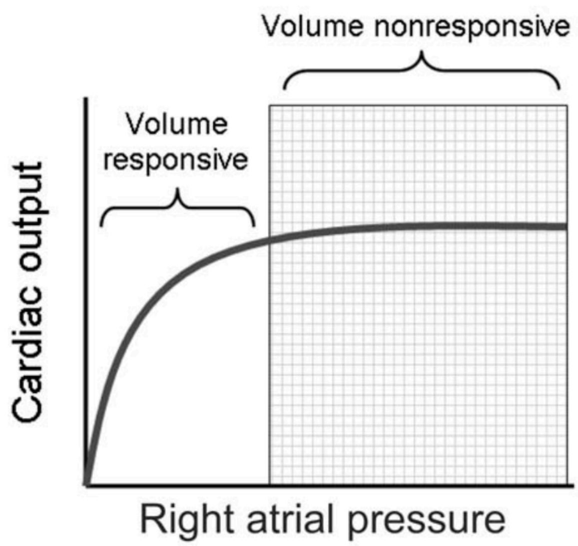

Figure 1. Fluid Status as Predicted by the Starling Curve.
Note: The area indicated by the boxes is the point at which a fluid status no longer increases stroke volume and therefore does not improve cardiac output. Patients in this zone are considered unresponsive to fluid.

unacceptable in a publication from Crichtley and Crichtley (1999). The authors evaluated technology, through meta-analysis, which measured cardiac output and determined a bias and precision statistic of less than 30% should be considered standard. The authors concluded that limits of agreement and percentage error should be reported when conducting such research (Critchley & Critchley, 1999). Moreover, "acceptance of a new technique should rely on limits of agreement of up to +/- 30% (Critchley & Critchley, 1999).

With technological advancement and improved understanding of the parameters, publications began to appear touting the accuracy of the dynamic measurements. In 2011, Zochios et al. reported that dynamic measurements were superior to static measurements. The authors reviewed the literature to date and concluded that accessibility to these measurements and the evidence of their accuracy made them ideal for managing fluid therapy. At the time, however, evidence pointing to long-term outcomes was limited, and further studies were encouraged (Zochios & Wilkinson, 2011). To that end, and with the acknowledgment that there was limited data on the impact of dynamic measurement use peri-operatively on outcomes, Lakshmi et al. (2016) looked at 60 patients who underwent abdominal surgery with the aim of evaluating outcomes. The subjects were randomized into two groups; one with fluids managed with the use of CVP, maintained between 10-12 mmHg and one with fluids managed with SVV, where a change of 10% or more was demonstrated after fluid challenge. Outcome measures were length of stay in the intensive care unit (ICU) and total hospital stay. The findings reported a significantly shorter ICU stay in the SVV group. However, despite a shorter total hospital length of stay in the SVV group, the numbers were not significant. Additionally, total fluids administered were lower in the SVV group and other measured outcomes, such as use of blood products and colloids as well as urine output, remained comparable (Kumar, Rajan, & Baalachandran, 2016).

There is one early study that specifically looks at the PPV dynamic measurement in patients undergoing hepatic resection. Solus-Biguenet (2006) evaluated the accuracy of PPV, both invasive (radial and pulmonary artery) and non-invasive (infrared photoplethysmography and pulse oximetry waveform). Eight patients undergoing hepatic resection were given a total of 54 fluid challenges in the form of 250cc boluses of colloid. Increase in stroke volume index of 10% or more was considered fluid responsiveness. The authors reported that PPV invasive and noninvasive were accurate measurements of fluid responsiveness (Solus-Biguenet et al., 2006). Artifact and the lack of real-time readings in the noninvasive PPV measurements underscored the need for the technology to evolve. Despite the findings, it is possible that the limitations explain the rationale for dynamic measurements not to be considered standard of care at the time.

Goal-Directed Fluid Therapy (GDFT)

Fluid management with the aim to optimize cardiac output in an effort to maximize oxygen delivery to the organs and tissues has been the topic of many research studies (Mythen Monty et al., 2012). As posed in an editorial that appeared in *The British Journal of Anaesthesia* in 2006, the debate regarding fluid overload and fluid restriction has not been settled (Bellamy, 2006). The author described early implementation of efforts to optimize outcomes through fluid therapy and suggested the limits to the early trials were inconsistencies in the timing and delivery of fluid interventions (Bellamy, 2006). The trial in question was conducted by Shoemaker et al. (1973) at the St. James University Hospital, Leeds, UK. The authors evaluated the hemodynamic patterns of 98 patients who were exposed to major surgical procedures and whose conditions were considered life-threatening. Based on the findings, the authors developed what they considered acceptable parameters in cardiac output, mean arterial pressure, pulmonary vascular resistance, arterial blood pO2, pH, and oxygen consumption that were associated with survival (Shoemaker, Montgomery, Kaplan, & Elwyn, 1973).

A study conducted by Thacker (2016) evaluated the perioperative fluid management and associated outcomes in common surgical cohorts in the United States (Thacker, Mountford, Ernst, Krukas, & Mythen, 2016). The authors suggested that there was no current consensus on fluid use or the effects of fluids on outcomes in the United States. A query was made of the Premier Research Database ("Customized healthcare studies from Premier Research Services - Premier, Inc.," n.d.) for cases between January of 2008 and June of 2012. Data were analyzed for a total of over 650,000 patients receiving colon, rectal, hip or knee surgery regarding fluid utilization on the day of surgery. They analyzed this information related to length of stay, total costs, and postoperative ileus. High fluid volume was associated with increased length of stay, increased total costs and postoperative ileus in the rectal and colon surgery cohorts. The findings also showed low fluid utilization was associated with "worse outcomes" (Thacker et al., 2016). Figure 2 is an illustration that suggests fluid optimization leads to optimal outcomes.

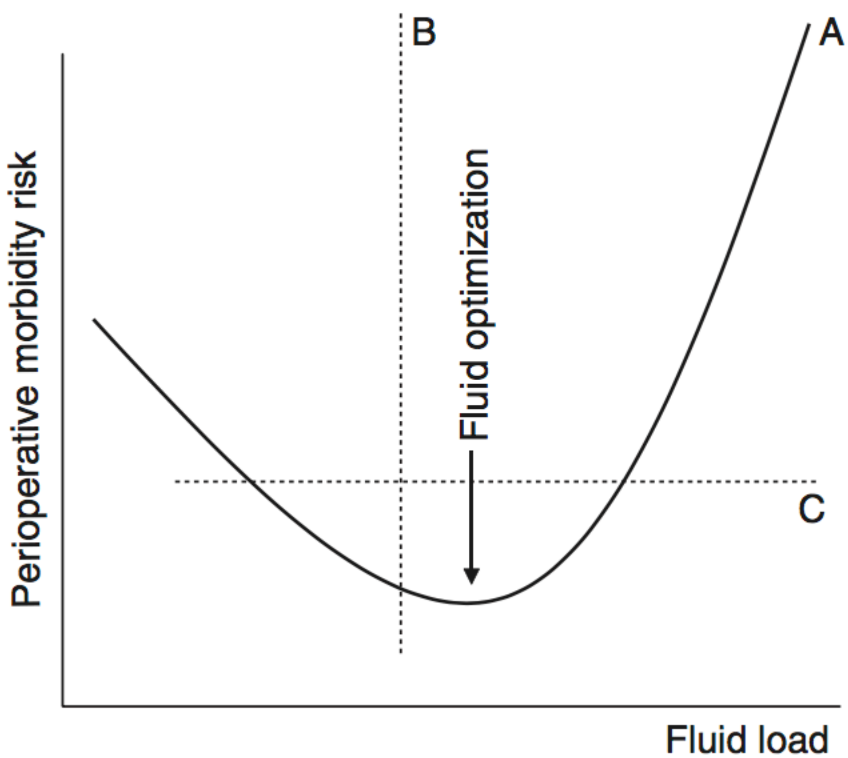

Figure 2. A Comparison of Perioperative Morbidity Risk and Fluid Status.

A possible explanation for the lack of utilization of dynamic measures and subsequent popularity is suggested by Marik (2009) whose previously mentioned meta-analysis suggested that these measurements were only possible with an anesthetized and mechanically ventilated patient (Marik et al., 2009).

Researchers in other countries endorse the use of goal-directed therapy as a sole tool to optimize patient outcomes as well as an integrated part of enhanced recovery after surgery protocols as first described by Henrik Kehlet of Denmark (Kehlet, 1997). A consensus statement was published in 2009 and updated in 2012 from the Enhanced Recovery Partnership; a group put together by the Department of Health in England in May of 2009 to promote enhanced recovery protocols designed to improve patient outcomes (Mythen Monty et al., 2012). The statement was published as a set of general principles and key recommendations based on the authors' experience. The authors conceded that "larger, more definitive studies of perioperative fluid management and, in particular, the relative contribution of hemodynamic monitoring compared with fluid restriction would be welcomed" (Mythen Monty et al., 2012). They also stipulated that such research must be conducted where enhanced recovery protocols are embraced. Another consensus statement was issued in 2015 by the international Fluid Optimization Group. Once again, the statement emphasized that over-hydration and under-hydration were deleterious and acknowledged a variability in practice. The group's intent was to point out the risks and benefits GDFT through evidence to reduce variability in practice (Navarro et al., 2015). The international Fluid Optimization Group consisted of 14 researchers from 7 countries. They conducted a review of 162 fluid resuscitation papers from both operative and intensive care unit settings. The consensus statement was the product of 3 years of discussions and analysis of the risks and benefits of various methods of fluid management. The authors concluded that fluid should be managed on an individual basis based on the patients' level of fluid responsiveness and the consensus report included approaches and practical recommendations to that end (Navarro et al., 2015).

In 2017, Michard et al. published a paper evaluating the accuracy of uncalibrated dynamic monitors as used for the purpose of GDFT. The authors suggested that to date, methods for assessing dynamic fluid status were predominantly done with calibrated pulse contour measurements and/or pulmonary catheters or esophageal dopplers (F Michard, Giglio, & Brienza, 2017). Nineteen studies were evaluated that included 2159 patients. The authors reported a reduction in postoperative morbidity, an increase in colloid administration and a decrease in crystalloid administration with the use of GDFT. Total fluid administered, and variability of fluid volume was not influenced by the use of GDFT. Finally, the authors concluded that the use of un-calibrated pulse contour techniques was associated with a decrease in postoperative morbidity (F Michard et al., 2017).

A 2014 publication by Dunki-Jacobs, et al. assessed the accuracy of GDFT in hepatic resection patients. The investigation included 80 patients in two cohorts and simultaneously compared CVP to SVV prospectively. The authors concluded that SVV is a safe and effective alternative to CVP measurement during hepatic resection. It was also suggested that SVV offered an option that eliminated risks associated with insertion of CVC for the purposes of monitoring CVP (Dunki-Jacobs, Philips, Scoggins, McMasters, & Martin, 2014). A limit to the study, however, is the authors did not separate open cases from laparoscopic.

In 2015, Correa-Gallego published a paper dealing specifically with the use of GDFT in uncalibrated pulse contour measurement devices in a population of patients undergoing hepatic resection. The authors conducted a prospective study that included 136 patients in two cohorts; GDFT and standard perioperative fluid management. The findings suggested that the use of SVV to manage perioperative fluids in patients undergoing partial hepatectomy resulted in patients receiving less fluid. It was also reported that there was a relationship between lower intraoperative fluid volumes and a decrease in postoperative morbidity for all patients (Correa-Gallego et al., 2015).

Associated complications

Blood transfusion during hepatic resection has become less frequent due to improved surgical and anesthetic techniques for hepatic resection (Day et al., 2016). In general, blood transfusion has been associated with poor outcomes, at the forefront of which is transmission of communicable disease (Jarnagin et al., 2008). Of particular importance in the cancer patient population is the effect of immunosuppression, which has been well documented since the early 1980s when the human immunodeficiency disease was first described (Porembka, 2001).

A study conducted by Gascon (1984) evaluated natural killer cell activity post-transfusion comparing 50 normal individuals to 79 individuals with disorders requiring multiple transfusions over time. The authors reported that those individuals who received blood transfusions had a significantly decreased natural killer cell activity proportional to the amount of blood transfused (Gascon, Zoumbos, & Young, 1984). In 2003, Kooby et al. examined blood transfusion records and outcome of 1351 patients who underwent hepatic resection for metastatic colorectal cancer over a 15 year period at Memorial Sloan Kettering Cancer Center(Kooby et al., 2003). The authors made a point of disclosing the conflicting evidence in the literature regarding the effects of transfusion on outcomes in patients with cancer citing eight meta-analyses. Transfusion of any blood products within a 30-day period of the surgical procedure was considered a transfusion. A grading scale of 1-5 was used where grades 3-5 were considered major and used for analysis. Fifty-five percent of the population received a blood product. The authors took note that early in the time frame analyzed, transfusion rates were 83% and this number dropped by the end of the time frame to 43%. The authors reported that patients who received blood transfusions had longer length of stay and decreased survival rate. The authors concluded that blood conservation methods should be used to minimize transfusion of blood products due to the relationship with poor outcomes (Kooby et al., 2003).

In 2008, Jarnagin et al. conducted an investigation addressing the issue of transfusion with acute normovolemic hemodilution (ANH). The sample included 130 patients who underwent hepatic resection involving more than three lobes of the liver. The target of the intervention arm was a hemoglobin of 8 g/dl. LCVP anesthetic technique was used in both arms of the investigation. The patients in the ANH arm received 50% fewer transfusions when compared to those in the standard care group. The authors reported that there was no difference in complication rate between the two arms. Despite the 50% reduction in transfusion requirements in the ANH group when compared to standard care, statistical significance was not achieved. The authors attribute this to the low transfusion rate in the standard care arm (25.4%) when compared to the anticipated/general population (40%). A proposed possible reason for this is under powering of the investigation. The conclusion drawn from the investigation was that ANH was a safe and effective method for decreasing likelihood of transfusion in patients undergoing major hepatic resection (Jarnagin et al., 2008).

Surgical site infection (SSI), is a common yet preventable complication following hepatic resection (Okabayashi et al., 2009). In 2014, Yang et al. reviewed charts from 7,388 patients who underwent hepatic resection. Six hundred ninety-eight patients developed SSIs. Post-operative stays for patients who developed SSI was significantly longer (13.6 days compared to 7.2) than those who did not. The authors identified groups from the population who were high risk for developing SSI. These groups were those with hepatolithiasis and those with cirrhosis. The authors concluded that an effort should be made to treat the high-risk groups with caution and to minimize blood loss (Yang et al., 2014).

Adjunct efforts to curb blood loss.

Antifibrinolytics. In addition to LCVP, bed position (reverse Trendelenburg) and improved surgical techniques, there are other adjunct tools the surgeons utilize to minimize perioperative blood loss. One of these methods is the use of antifibrinolytics. One such adjunct is the medication tranexamic acid (TXA), a synthetic derivative of lysine that exerts its effects by binding to plasminogen (Carless, Rubens, Anthony, O'Connell, & Henry, 2011). The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH 2) trial was conducted beginning in 2005 by 274 hospitals in 40 countries. Patients were enrolled based on the uncertainty principle, that is if the responsible health care provider was uncertain as to whether or not to treat with TXA. Participants and health care providers were blinded to the treatment arm, TXA or placebo. A total of10,060 TXA and 10,067 placebo recipients were analyzed. The results of the study revealed that early administration of TXA to individuals at risk of significant blood loss was associated with reduced risk of death from hemorrhage. Additionally, all-cause mortality was significantly (32%) reduced with TXA. The authors suggested the findings support the use of TXA in a wide range of health care settings, and safely reduced the risk of death in bleeding trauma patients (Williams-Johnson, McDonald, Strachan, & Williams, 2010).

The use of TXA in hepatic resection is not well documented in the literature. In 2006, Wu et al. conducted a double-blind randomized trial with 214 participants who underwent hepatic resection. One hundred eight participants received TXA, and one hundred six received placebo. The authors reported that operative blood loss was reduced and small vessel venous bleeding could be controlled with compression and not suturing due to the effect of TXA (Wu et al., 2006). The authors concluded with a suggestion that blood transfusion during hepatic resection could become a rare occurrence with the assistance of TXA (Wu et al., 2006).

In a study conducted by Karanicolas et al. (2016) a sample of 18 was divided into three cohorts to investigate two dosing protocols. The authors' aim was to assess the impact of TXA on hyperfibrinolysis that occurs due to systemic inflammation or hepatic injury during major hepatic resection (Karanicolas et al., 2016). The authors utilized serial blood samples and measured thromboelastography (TEG), coagulation components and the concentration of TXA. The findings were negative for TXA influence on levels of TEG and plasmin-antiplasmin complex. The authors suggested that local parenchymal surface fibrinolysis may be affected by TXA and further studies should be conducted to assess such an impact at a cellular level (Karanicolas et al., 2016).

Topical agents. Another adjunct to control bleeding are topical agents which include fibrin sealants, collagen, gelatin and cellulose sponges and/or a combination of products. As described in an overview of hemostasis techniques for patients undergoing hepatic resection, fibrin sealants have mixed support. Berrevoet (2007) suggested that fibrin sealant enhances clot formation but may also aid in minimizing post-operative biliary leaks and fistula formation (Berrevoet & de Hemptinne, 2007). In 2002, Henry et al. evaluated 12 trials where fibrin sealants were utilized to control intraoperative bleeding. The authors conceded that the trials that met inclusion criteria were small and of poor methodological design. Their results suggested that fibrin sealants were effective in controlling blood loss but large-scale trials were encouraged (Carless et al., 2011). Figueras et al. (2007) published a paper evaluating the efficacy of fibrin sealants on hemorrhage, biliary leakage and post-operative complications in patients who underwent partial hepatectomy. The sample size included 300 patients who were randomized to receive topical fibrin intraoperatively or standard care control. The authors reported that there were no differences between the groups regarding transfusions. There were no differences between the groups in leakage rates as well. Additionally, there were no differences in the incidence of biliary fistula and/or mortality. The publication concluded with a suggestion that the use of fibrin sealant for the purpose of minimizing blood loss, leakage and improving post-operative outcomes was unjustified and that discontinuing the practice of using such methods for the stated purposes would be a cost-saving maneuver (Figueras et al., 2007).

Other blood component factors. Recombinant factor VIIa has also been investigated as a prophylactic drug to minimize blood loss during partial hepatectomy. Alkozai et al. (2008) concluded that this drug might better serve as a "rescue therapy" for use in uncontrolled bleeding when other methods have failed (Alkozai, Lisman, & Porte, 2009).

Rationale for changes in the LCVP technique over time

Since first developed as an anesthetic technique in the early 1990s at Memorial Sloan Kettering Cancer Center and described by Cunningham et al. (1994), the LCVP technique has evolved in response to evidence-based changes in practice over time. In the early 2000s, the use of heavy narcotics (up to 30mg of intravenous morphine and 500mcg of intravenous fentanyl) for the purposes of lowering CVP were abandoned in favor of the use of intravenous and then sublingual nitroglycerin. This change in technique allowed for the patients to be extubated before arrival in the post-anesthesia care unit (PACU). A 2009 publication from Hammoud et al., evaluated 228 patients who underwent major orthopedic surgery. The authors explored the synergistic effects of morphine with other adjunct pain medications and concluded that 20 mg of morphine or more administered in the immediate postoperative period was associated with an increase in sedation and delay in extubation (Hammoud et al., 2009). Application of this knowledge to other specialties such as hepatobiliary patients has improved outcomes in the form of minimizing time spent on a mechanical ventilator, which in and of itself is associated with poor outcomes. A study by Nobili et al. (2012) evaluated 555 patients who underwent hepatic resection. The purpose of their study was to assess for risk factors associated with postoperative pulmonary complications. The retrospective data were analyzed with particular attention to poor outcomes regarding pleural effusion, pneumonia and pulmonary embolism. The authors suggested that postoperative pulmonary complications were associated prolonged hospital stay and more frequent intensive care unit admissions (Nobili et al., 2012). To this end, decreasing the time a patient is mechanically ventilated may improve outcomes by minimizing risk factors associated with postoperative pulmonary complications.

Alternative approaches to pain control include incisional injection of local anesthetics, transverse abdominus plane (TAP) blocks and epidural catheter injection of morphine and local anesthetics. A recent study by Aloia, et al. (2017) included 146 patients who underwent hepatic resection and compared thoracic epidural analgesia (TEA) with intravenous pain-controlled analgesia. The authors concluded that TEA was more effective than intravenous controlled analgesia, the patients required less intravenous morphine, had superior pain control and demonstrated comparable length of stay (Aloia et al., 2017).

Alternatively, surgeons may opt to perform hepatic resections laparoscopically. Benefits of laparoscopic liver resection (LLR) have been described to include decreased intraoperative bleeding, transfusion requirements, as well as lowering incidence of postoperative ascites (Egger et al., 2017). In 2017, Egger et al. published an overview of the preoperative, perioperative and postoperative anesthetic consideration for patients who LLR has been deemed appropriate. The popularity of performing LLR has increased, however as the authors point out, the learning curve is steep, and selection of appropriate candidates is imperative (Egger et al., 2017).

Enhanced recovery after surgery (ERAS) protocols have become popular of late. ERAS is a comprehensive pathway that surgical patients are put on to optimize treatments and minimize poor outcomes related to said treatments. They capitalize on preemptive treatment of potential side effects surgery and anesthesia, early ambulation and discharge. In the oncologic population, these goals help to minimize the interruption of cancer treatment when surgical intervention is necessary. In 2015, a study conducted by Day, et al. at MD Anderson compared 75 patients who were on an ERAS pathway with 43 patients who were treated with standard care. The pathways included patient education, reduction in use of narcotics during anesthesia and for analgesia, early return to normal diet, fluid restriction, early ambulation and limited use of drains. The patients rated severity of life interference preoperatively and postoperatively. The authors suggested that use of ERAS pathways in patients undergoing hepatic resection was beneficial in that it allowed for improved patient satisfaction and early return to oncological treatments (Day et al., 2015)

Evolution of LVCP at MSKCC.

Around 2008, the LCVP technique became somewhat of a misnomer because CVP was phasing out as a valued measurement of fluid status. Central venous catheters were no longer routinely placed in patients undergoing partial hepatectomy. At that time there was a move to dynamic measurements, and this modification to the LCVP technique was described and previously presented in this paper as the study conducted by Correa-Gallego in 2015 (Correa-Gallego et al., 2015).

Kingham et al. (2014), published a paper looking at three phases in time regarding the outcomes of patients undergoing partial hepatectomy at Memorial Sloan

Kettering Cancer Center. The authors evaluated 4152 patients and assessed the changes in morbidity and mortality from 1993 to 2012 at one institution. The authors reported that morbidity and mortality had decreased. They attributed the improved outcomes to changes in surgical technique, prevention of SSI and increased alternative techniques for treating liver cancer (Kingham et al., 2015). The authors failed to account for change in anesthetic technique, specifically, early extubation, limited use of central venous catheters and change in fluid management.

Application of Theory

Avedis Donabedian described a framework for assessing the quality of care using the linear relationship between structure, process, and outcomes. (Donabedian, 1978). These constructs allow investigators to clearly describe what is being assessed and their influences can be exerted in multiple directions. Additionally, Donabedian's theory affords an explanation of relationships. These are two qualities considered standard elements in theory (Goes & Simon, 2012). According to Goes and Simon (2011), theories exist as a belief regarding reality. A theory's purpose is to "describe, explain, predict, or understand human or social phenomena in a variety of contexts (Goes & Simon, 2012)

Constructs.

Donabedian's first approach to assessing quality of health care focuses on structure. This is the setting in which the care is delivered. Here he is focusing on "adequacy of facilities and equipment; the qualifications of medical staff and their organization; the administrative structure and operations of programs and institutions providing care; fiscal organization and the like" (Donabedian, 1978). Assumptions such as given proper settings and instrumentalities, good medical care will follow, must be avoided (Donabedian, 1978). Donabedian conceded that a major limitation when assessing structure is that the relationship between structure and process and structure and outcome, is often not well established (Donabedian, 1978).

Donabedian also looked at assessing the process of care itself. This is the application of medical knowledge to medical care or whether medicine is being properly practiced. Russell (1998) points out that it is important to determine whether the process is fully documented and standardized because, "if it is not, it will not be possible to say which components are the cause of any variations in outcomes, and therefore attribution remains approximate and an unsound basis for changing the provision of care"(Russell, 1998). This is in keeping with Goes & Martin's (2012) assessment of standards for evaluating theory and their emphasis on internal and external consistency.

Finally, Donabedian examined outcomes. The advantages of measuring outcomes is that validity of outcome as the criterion of quality is seldom questioned. There is no doubt about the stability and validity of the values of recovery, restoration and survival in most situations (and most cultures but not in all). Finally, outcomes tend to be concrete, amenable to more precise measurement (Donabedian, 1978).

Limits to outcome measurements include the possibility that a particular outcome may be irrelevant, such as when survival is chosen as a criterion of success in a situation which is not fatal but is likely to produce suboptimal heal or crippling conditions. Many factors other than medical care may influence outcomes, and they must be held constant if valid conclusions are to be drawn

In some cases, long periods of time (decades) must elapse before relevant outcomes manifest. Results may not be available when they are needed for appraisal, and the problems of maintaining comparability are greatly magnified (Donabedian, 1978). An example of a linear relationship between the constructs of Donabedian's theory is illustrated in Figure 3.

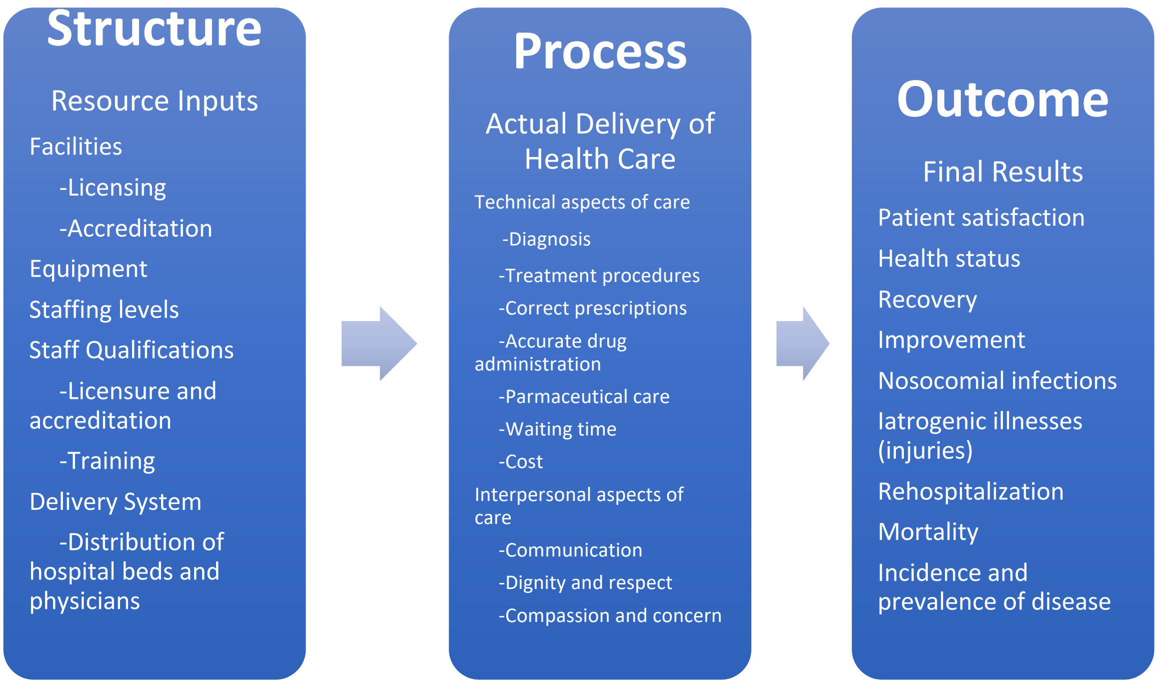

Figure 3. The Constructs of Donabedian's Theory (Shi & Singh, 2015).

Greater specificity of variables allows the research team to exercise much greater control over what dimensions of care require emphasis and what the acceptable standards are (Donabedian, 1978). This is also an element of a theory that Goes and Simon (2012) refer to as 'simplicity' (Goes & Simon, 2012).

Measurement

The Donabedian theory also takes into account reliability of assessments. The major mechanism for achieving higher levels of reliability is the detailed specification of criteria, standards, and procedures used for the assessment of care (Donabedian, 1978). Consistency between assessors is important as is consistency with one assessor over time. Reliability can also be improved with reproducibility.

Donabedian believed that process elements could be used as indicators of quality only if there is a valid relationship between those elements and desired outcomes(Donabedian, 1978). For instance, it is important to account for other factors that may be related to the outcome of interest so as not to skew the findings. In other words, establishing a relationship between the two variables as independent improves validity. Donabedian also stated that specific outcomes could be used as indicators of the quality of care only to the extent that there is a valid relation between the two. In effect, validity resides not in the choice of the elements of process or the outcome but in what is known about their relationship (Donabedian, 1978).

Donabedian's theory applies to this dissertation in a fashion which overtly utilizes two of the constructs; process (utilization of central venous catheter) and outcome (complications). This example shown in figure 4 as actual delivery of health care and the relationship, or impact it has on final outcomes. The application of Donabedian's theory does not necessitate the use of all three constructs, structure, process and outcome. However, it could be argued that for this project MSKCC is a structure concept where the data is being generated, and therefore, all three constructs are in play as shown in Figure 4.

Using the Donabedian theory to address this issue also demonstrates this theory's ability to show practicality as well as acuity, the final two standards mentioned by Goes and Simon (2012). In doing so, one will be able to provide insight into an otherwise complex issue with real-world application (Goes & Simon, 2012).

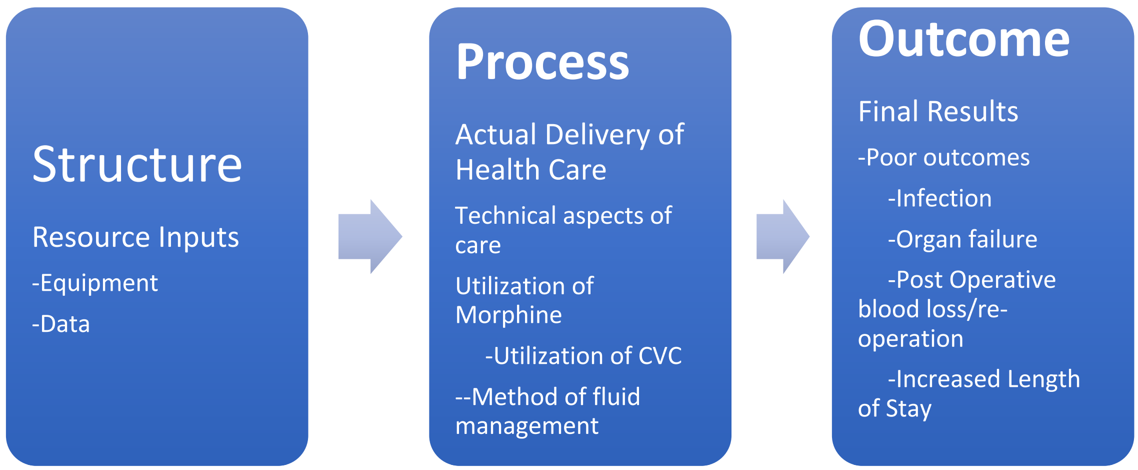

Figure 4. Application of Donabedian Constructs.

Hypotheses

In this study, there are five hypotheses under investigation based on the Donabedian theory. The constructs of structure, process and outcome are implemented in the form of the proposition that changes in patient care lead to changes in patient outcomes.

- Hypothesis one (H_1): There is a relationship between the use of a central venous catheter and patient outcomes for patients who have undergone partial hepatectomy.
- Hypothesis two (H_2): There is a relationship between time of extubation following partial hepatectomy and patient outcomes.
- Hypothesis three (H_3): There is a relationship between use of intraoperative morphine for the purposes of LCVP and outcomes for patients who have undergone partial hepatectomy.

A review of the literature shows no research addressing whether there is a relationship between the evolution of LCVP technique and outcomes for patients undergoing hepatic resection.

Chapter 3: Methods

Guided by Donabedian's theory assessing the quality of health care, this chapter presents the methods and analytical approach to addressing the core hypothesis and research question regarding a relationship between presence of a central venous catheter in patients undergoing partial hepatectomy at a single, high volume institution and outcomes.

The stated objectives of this research project are to assess whether there is a relationship between a) insertion of intraoperative CVC and selected outcomes in patients undergoing hepatic resection, b) the use of morphine for the purpose of lowering CVP for hepatic resection and selected outcomes, and c) extubation in the OR and outcomes in patients undergoing hepatic resection. A summary of the purpose, objectives, and research hypotheses is provided in Table 2.

Methodology/Approach

This project is a non-randomized, non-experimental, retrospective, cohort design. Retrospective designs involve collecting data about an outcome in the present and then looking back in time for possible relationships (Polit, 2006).

Research Design

The independent variables are presence of CVC and use of morphine for the purposes of LCVP anesthetic technique and extubation of patients in the OR for patients undergoing hepatic resection. The dependent variables are selected outcomes

Table 2. *Summary of Purpose, Objectives and Hypotheses*

Purpose	**Objectives**	**Research Hypotheses**
to examine the data from MSKCC with an updated time frame (2006-2016) in an effort to clarify if change in anesthetic technique over time had an impact on selected outcomes	to assess whether there is a relationship between insertion of intraoperative CVC and selected outcomes in patients undergoing hepatic resection	H_1 There is a relationship between the use of a central venous catheters and patient outcomes
	To assess whether there is a relationship between the use of morphine for the purpose of lowering CVP for hepatic resection has and selected outcomes.	*(H_2):* There is a relationship between use of intraoperative morphine for the purposes of LCVP and patient outcomes
		(H_3): There is a relationship between time of extubation at the end of the procedure and patient outcomes

and are included in Table 3. More than one complication in the same category will only be counted once.

Demographic data will also be collected. These items are included in Table 4. Surgical procedures are delineated in Table 5.

All patients will have undergone general anesthesia. All medications administered as well as all captured vital signs will be included for analysis. Other data collected will be intravenous crystalloid, intravenous colloid, intravenous blood products, urine output, estimated blood loss, and adjunct coagulation products such as topical antifibrinolytics.

Table 3. *Postoperative Complications*

Organ System	Specific Complication
Liver/biliary	
	Hepatic insufficiency/failure
	Sterile perihepatic fluid collections
	Biliary Stricture
	Cholangitis
Pulmonary	
	Pleural effusion
	Atelectasis
	Respiratory insufficiency/failure
	Pulmonary embolism
Cardiovascular	
	Arrhythmia
	Deep vein thrombosis
	Congestive heart failure
	Angina pectoris/myocardial infarction
	Cardiac arrest
	Stroke/TIA/CNS hemorrhage
	Pericarditis/pericardial effusion
Genitourinary	
	Renal insufficiency
	Urinary retention
Gastrointestinal	
	Ileus
	Bowel obstruction
	Gastrointestinal hemorrhage
	Colitis (includes *C. diff*)
	Bowel perforation
Infection	
Abdominal	Wound infection
	Perihepatic abcess
	Bile leak/biloma
Nonabdominal	
	Sepsis/bacteremia
	Urinary tract infection
	Pneumonia
Miscellaneous	
	Perioperative hemorrhage
	Delirium
	Wound breakdown/fascial dehiscence
	Ascites
	Pump dysfunction
	Multisystem organ failure

Table 4. *Demographic Data*

Variable	Measurement
Age	Years
Sex	M/F
Comorbidity %	1, 2, >/= 3

Table 5. *Surgical Procedures*

Procedure	
Major hepatectomy	>/= 3 segments
Segments resected	n
Left hepatectomy	
Left trisesectionectomy	
Right hepatectomy	
Posterior sectionectomy	
Right trisectionectomy	
Resection combined with ablation	

Selection of Subjects

The population under investigation is patients who have undergone partial hepatectomy. The number of cases in the sample was be limited to the number of cases performed at MSKCC. MSKCC surgeons perform nearly such 400 cases annually. Therefore, the sample size wass expected to be 400 per year over the 10-year period and all cases between 2007 and 2016 meeting inclusion criteria were analyzed. The investigation will took place at MSKCC.

The rationale for the sample population is convenience as the PI is employed at MSKCC and this institution is does a high volume of hepatic resections annually. Inclusion and exclusion criteria are described in Table 6.

Table 6. *Inclusion and Exclusion Criteria*

Inclusion Criteria	Exclusion Criteria
18 years of age and older	<18 years of age
Undergoing partial hepatectomy at MSKCC	Infection/sepsis at time of admission
	Admission for other reason than partial hepatectomy
	Previous hepatic resection

Instrumentation

Tests and measures were that of standard practice at MSKCC. Aforementioned variables were recorded in the patient's electronic medical record as described in Table 7.

Table 7. *Description of Instrumentation*

MSKCC
Information comes from Optime/EPIC
Vital Signs and all intraoperative information are captured on:GE B850 Monitor ->GE Unity ->Excel BedmasterEx ->Rhapsody HL7 interface engine -> EPIC
All laboratory values are captured in Allscripts CIS
All assessments are obtained from Optime EMR

Data Collection and Recording

Data was a compilation of documents regarding patient hospital stay from admission forms to intraoperative records and EMR which includes official discharge date. The information was recorded by a variety of health care professionals involved in the patients care in Optime/Epic at MSKCC.

Data collection was from January 2006 through December of 2016. Once successfully navigating the internal review board of MSKCC and VCUMC to obtain permission to access the database, the data was queried. Data was housed in CAISIS which is a surgery-run data warehouse. The research team abstracts and entered the surgical information into CAISIS and the data manager queried it out for the investigators as requested. It was queried from Access and exported it into Microsoft's excel. Data managers entered the information in dataline requests to internal database or ran separate queries through a dissimilarity analysis and representation (DARwin) program for windows to try to fill in the blanks for missing data. If those failed, the investigative team performed chart review for any missing data.

Data Processing and Analysis

Summary statistics were reported as median and interquartile range (IQR) for continuous variables. Categorical variables were reported as percentages. Comparisons were made with t-tests or Mann-Whitney tests depending on type of distribution for continuous variables. Categorical variables were compared with chi-squared or Fisher's exact test, based on number of observations. Univariate and multivariate analyses used logistic regression. Comparisons with complications were analyzed using Poisson regression. All reported p values will be 2-tailed and those < 0.05 are considered significant. Data analysis was performed with IBM's SPSS version 24.

Findings were written in prose and included tables for values that show signs of significance to better illustrate the relationships.

Methodological Assumptions

All methods of measurement were considered valid. Additionally, health care professionals were assumed to be equally competent and proficient in delivering health care to the sample population under investigation. Finally, was assumed that infection rates/complication rates at any given time do not influence infection rates/complications from any other given time.

Limitations

Disadvantages of a retrospective study design include limited control of the investigator over the approach to sampling and follow-up population, and the nature and quality of the baseline measurements. The largest disadvantage of this investigation is that it is not possible to infer causality from the results. Additionally, the data may be incomplete, inaccurate, or measured in ways that are not ideal for answering the research question(s) (Hully et al., 2013). It may be assumed that the individuals who collected the data were equal however, the ability to rule out personal bias based on experience and its influence on measurements cannot be ignored.

Summary

Chapter three included a discussion of the methods utilized in this non-randomized, non-experimental, retrospective, cohort study. A description of the study plan to assess whether there is a relationship between a) insertion of intraoperative CVC, b) the use of morphine for the purpose of lowering CVP c) the extubation of the patient in the OR and outcomes in patients undergoing hepatic resection was described. Also provided was information regarding sampling methods, variables, data collection and management, statistical analysis, assumptions and limitations of the study.

Chapter 4: Results

The low central venous pressure (LCVP) technique, first described in 1994 by Cunningham, et al (Cunningham et al., 1994) at Memorial Sloan Kettering Cancer Center has evolved over these last 20 years. The purpose of this research was to explore effects of several changes to the LCVP technique on patients undergoing hepatic resection. In this study, relationships between use of morphine, insertion of central venous catheter (CVC) and total fluids administered, and outcomes were explored.

A non-randomized, non-experimental, retrospective, cohort design was used to meet three study objectives: to assess whether there is a relationship between a) insertion of intraoperative CVC and selected outcomes in patients undergoing hepatic resection, b) the use of morphine for the purpose of lowering CVP for hepatic resection and selected outcomes, and c) extubation of the patient in the OR and outcomes in patients undergoing hepatic resection.

Data allocation and preparation and statistical analysis exploring the relationship between the variables is described in chapter four. The chapter begins with a description of the variables and the process of cleaning the data for analysis. A summary of the statistical results regarding the individual objectives follows.

Data

Review of data acquisition

Following IRB approval from VCU and MSKCC, data was obtained from the January 1, 2007 through December 31, 2016. A total of 3903 (n = 3903) patients were initially to be included in the analysis. The anesthesiology database included 2958 cases and after cases were eliminated due to missing data the final sample size was 2518.

Data preparation and cleaning.

Data was combined by the primary investigator using an Excel spreadsheet. Data was inspected for accuracy of input and assigned as either binary or continuous for the purposes of analysis.

All variables were assessed for normality of skewness and kurtosis, and distribution. Additionally, outliers were identified, and assumptions assessed.

All data was obtained from the hepatobiliary and anesthesiology databases located at MSKCC. The data dated from January of 2006 to December of 2016. Figure 5 describes the impact of cleaning the data in preparation for analysis on the sample size.

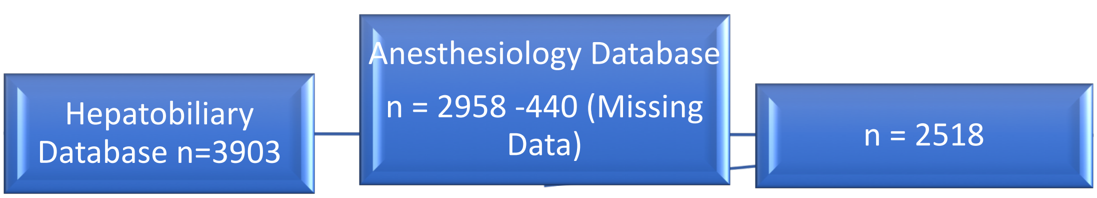

Figure 5. Impact of Data Cleaning.

Data Analysis

The following section describes variables in the final analysis. The data of 2518 cases provided evidence regarding the research hypotheses being tested (H_1-H_3). The hypotheses address relationships between presence of a CVC, use of morphine, and extubation, on postoperative infections, and other complications in patients undergoing hepatic resection. Table 8 includes the definitions of the variable abbreviations as they appear in the analysis.

Table 8. *Variable Abbreviation Definitions.*

DOS	Date of Surgery
PROC_NAME	Procedure Name
FEMALE	Female
AGE	Age
EXT	Extubated in OR
TOTAL	Total Fluids
CVP	Central Venous Line
MS	Morphine Sulfate
AMT	Morphine Sulfate Amount
MORT90D	90 Day Mortality
NUM_COMP	Number of Complications
NUM_SEVERE_COMP	Number of Severe Complications
WOUND_INF	Superficial Wound Infection
INT_ABD_INF_ABC	Intra-Abdominal Infection or Abcess
NUMBER OF CO MORB	Number of Comorbidities
TOT NUM SEGS	Total Number of Segments
LAP	Laparoscopic

Univariate regression was used to assess whether specific relationships exist. Mulitvariate regression determined overall influence on outcomes. Additionally, a Poisson regression was used to assess the number of times that an event occurred in a specific interval of time.

Table 9. *Descriptive Statistics*

Continuous: Median (Min, Max)
Categorical: N (%)

	Overall
AGE	59 (18, 90)
TOTAL	2800 (0, 16750)
UOP	230 (0, 4000)
EBL	300 (0, 7800)
TOT_PROCEDURE_TIME	228 (1, 1136)
FEMALE	
0	1285 (51)
1	1233 (49)
EXT	
0	718 (28.5)
1	1800 (71.5)
EPI	
0	2345 (93.1)
1	173 (6.9)
CVP	
0	2107 (83.7)
1	411 (16.3)
MS	
0	1881 (74.7)
1	637 (25.3)
MORT90D	
0	2482 (98.6)
1	36 (1.4)
NUM_COMP	
0	1608 (63.9)
1	504 (20)
2	262 (10.4)
3	81 (3.2)
4	31 (1.2)
5	20 (0.8)

Table 9. *Continued*

Table 9. *Continued*

6	2 (0.1)
7	4 (0.2)
8	1 (0)
9	1 (0)
10	2 (0.1)
11	2 (0.1)
NUM_SEVERE_COMP	
0	2073 (82.3)
1	341 (13.5)
2	76 (3)
3	21 (0.8)
4	5 (0.2)
6	1 (0)
7	1 (0)
MAX_COMP_GRADE	
0	1608 (63.9)
1	159 (6.3)
2	306 (12.2)
3	408 (16.2)
4	13 (0.5)
5	24 (1)
WOUND_INF	
0	2436 (96.7)
1	82 (3.3)
INT_ABD_INF_ABC	
0	2370 (94.1)
1	148 (5.9)
BENIGN.0.MALIGNANT.1.	
0	74 (2.9)
1	2444 (97.1)
NUMBER.OF.CO.MORB	
1	2277 (90.4)
2	215 (8.5)
3	25 (1)
4	1 (0)

Table 9. *Continued*

NUMBER OF SEGMENTS	
<3	1624 (64.5)
>=3	894 (35.5)
LAP	
0	2323 (92.3)
1	195 (7.7)

included. After data cleaning a total of 2518 cases were analyzed of 3903 possible cases. The inability to include all cases is a known limitation of studies of this nature (Polit, 2006).

Descriptive Statistics

Descriptive statistics on the variables investigated in this study are presented in Table 9. For each, median, minimum and maximum/or percentage numbers are

Hypothesis Testing

Data was confirmed to not be in violation of assumptions of normality, linearity, homoscedasticity. Following this, the three hypotheses were tested.

Hypothesis one (H_1)

Hypothesis one (H_1) assessed for a relationship between the use of central venous catheters and outcomes for patients undergoing hepatic resection. Results for presence of CVC are shown in table 10.

- Hypothesis one (H_1): <u>There is a relationship between the use of central venous catheters and outcomes in patients undergoing hepatic resection.</u>

Hypothesis one was tested by univariate logistic regression and showed a 15%, odds ratio 1.15 (0.63-1.98, CI 95%) increase in wound infection, and a 10%, odds ratio 1.10 (0.7-1.67, CI 95%) increase in deep wound infection or abscess with the presence

Table 10. *Results for Presence of Central Venous Catheter*

Univariate Logistic Wound INF	Odds Ratio (95% CI)	p-value
CVC	1.15 (0.63-1.98)	0.624
Univariate Logistic Int Abd Inf or Abc		
CVC	1.1 (0.7-1.59)	0.673
Univariate Logistic 90D Mortality		
CVC	3.34 (1.66-6.52)	<.001
Poisson Regression-Number of Complications	Slope/ Estimates	p-value
No CVC	0.62	.122
CVC	0.69	
Poisson Regression-Number of Severe Complications		
No CVC	0.22	0.003
CVC	0.30	

of a central venous catheter. However, these results appear to be clinically significant, yet were not statistically significant with p-values of 0.624 and 0.673 respectively.

There was a significant relationship between use of central venous catheters and 90day mortality. An odds ratio of 3.34 (95% CI, 1.66-6.52) was demonstrated with univariate logistical regression (p-value <.001, CI 95%).

A Poisson regression analysis showed significance in central venous catheter (Slope/Estimate 0.22) versus no central venous catheter (Slope/Estimate 0.30) with a p-value of .003 in incidence of severe complications but no significant difference in complications over all. Significant findings from univariate regression were included in a stepwise multivariate regression, all were eliminated in that process.

Hypothesis two (H_2)

Hypothesis two (H_2) assessed for a relationship between the time of extubation and outcomes for patients undergoing hepatic resection. Results for extubation are shown in Table 11.

Table 11. *Results for Extubation*

Univariate Logistic Wound INF	Odds Ratio (95% CI)	p-value
Extubated in OR	0.68 (0.43-1.09)	0.102
Univariate Logistic Int Abd Inf or Abc		
Extubated in OR	0.85 (0.6-1.22)	0.368
Univariate Logistic 90D Mortality		
Extubated in OR	1.2 (0.58-2.71)	0.638
Poisson Regression-Number of Complications	Slope/ Estimates	p-value
Not Extubated in OR	0.58	
Extubated in OR	0.66	0.021
Poisson Regression-Number of Severe Complications		
Not Extubated in OR	0.21	
Extubated in OR	0.24	0.173

- Hypothesis two (H_2): There is a relationship between the time of extubation and outcomes in patients undergoing hepatic resection.

Hypothesis two was tested by univariate logistic regression and showed a 32%, odds ratio 0.68 (0.43-1.09, CI 95%) decrease in incidence in superficial wound infection and a 15%, odds ratio 0.85 (0.6-1.22, CI 95%) decrease in deep wound infection or abscess. Again, these results may be clinically significant but do not meet criteria for statistical significance.

Ninety-day mortality did not reach significance with a p-value of .638 and showed an odds ratio of 1.2 (0.58-2.71) which suggests a 20% increase in 90day mortality associated with extubation in the OR.

The Poisson regression for any complications shows a p-value of .021 (CI 95%). The results show that extubation in the OR was associated with slightly larger incidence of complications compared to extubated in the post anesthesia care unit, with slope/estimates of 0.66 compared to slope/estimates of 0.58.

The numbers for association with severe complications did not reach statistical significance with a p-value of 0.173 (CI 95%) and slope estimates of 0.24 and 0.21, extubated and not extubated respectively.

Significant findings from univariate regression were included in a stepwise multivariate regression, all were eliminated in that process.

Hypothesis three (H_3)

Hypothesis three (H_3) assessed for a relationship between the use of morphine for the purpose of LCVP and outcomes for patients undergoing hepatic resection. Results for use of morphine are in Table 12.

- Hypothesis three (H_3): <u>There is a relationship between the use of morphine for the purpose of LCVP and outcomes in patients undergoing hepatic resection.</u>

Hypothesis three was tested by univariate logistic regression and showed a 65% increase in superficial wound infection with an odds ratio of 1.65 (1.02-2.59, CI 95%), and a 10% increase in deep wound infection or abscess with an odds ratio of 1.1 (0.75-1.59, CI 95%). The p-values were 0.035 and 0.618 respectively.

Table 12. *Results for Use of Morphine*

Univariate Logistic Wound INF	Odds Ratio (95% CI)	p-value
Morphine Used	1.65 (1.02-2.59)	0.035
Univariate Logistic Int Abd Inf or Abc		
Morphine Used	1.1 (0.75-1.59)	0.618
Univariate Logistic 90D Mortality		
Morphine Used	0.84 (0.36-1.77)	0.669
Poisson Regression-Number of Complications	Slope/ Estimates	p-value
Morphine Used	0.68	
Morphine Not Used	0.50	<.001
Poisson Regression-Number of Severe Complications		
Morphine Used	0.25	
Morphine Not Used	0.19	0.011
Multivariate Analysis Number of Complications	Slopes	P-Value
Morphine	0.60	<.001

Univariate regression for 90day mortality and use of morphine did not show statistical significance. An odds ratio of 0.84 (0.36-1.77, CI 95%) suggests a 16% decrease which may be clinically significant.

A Poisson regression analysis showed significance with the use of morphine (Slope/Estimate 0.50) versus no morphine (Slope/Estimate 0.68) with a p-value of <.001 in any complications. Additionally, mulitivariate analysis shows significance, p-value <.001, slope 0.60 in number of complications.

Number of severe complications was also significantly associated with a protective effect with slope/estimates of 0.19 and 0.25 with morphine and no morphine respectively at a p-value of 0.003.

Incidental Findings

Incidental findings from the analysis suggest that there is a relationship between gender and outcomes. Univariate regression for wound infection showed a p-value of 0.007 with an odds ratio of 0.53 (0.33-0.83, CI 95%) for female. Univariate regression for deep wound infection or abscess was not significant as the p-value was 0.449 with an odds ratio of 0.88 (0.63-1.23, CI 95%) for female. Univariate regression for 90day mortality showed a p-value of 0.013 with an odds ratio of 0.4 (0.18-0.8, CI 95%) for female.

The Poisson regression analysis for number of complications was significant at a p-value of <.001 and a slope/estimate at 0.56 compared to 0.70 for male. Multivariate regression analysis demonstrated significance with a p-value of 0.010 and a slope of 0.88 for female. The Poisson regression analysis for severe complication was significant at a p-value of .002 and a slope/estimate at 0.20 compared to 0.26 for male. Finally, the multivariate analysis of female showed a significant relationship with number of complications (slope 0.88, p-value <.001). The results for female or male are shown in Table 13.

Further analysis of co-morbidities between the two groups using a Wilcox test showed a statistically significant difference between the groups with a p-value of <.001 (Table 14). These findings suggest that men have more co-morbidities than women in this population.

Ninety-day mortality, (OR 7.74, CI 95%), Deep wound infections (OR 1.78, CI 95%), were significantly associated with more than three segments of liver resected.

Table 13. *Results for Female vs Male*

Univariate Logistic Wound INF	Odds Ratio (95% CI)	p-value
Female	0.53 (0.33-0.83)	0.007
Univariate Logistic Int Abd Inf or Abc		
Female	0.88 (0.63-1.23)	0.449
Univariate Logistic 90D Mortality		
Female	0.4 (0.18-0.8)	0.0.013
Poisson Regression- Number of Complications	Slope/ Estimates	p-value
Male	0.70	
Female	0.56	<.001
Poisson Regression- Number of Severe Complications		
Male	0.26	
Female	0.20	0.002
Multivariate Analysis Number of Complications	Slopes	P-Value
Female	.88	0.010

Table 14. *Results for Male vs Female Comorbidities*

	Female	Male	p-value
Comorbidities			<.001
1	1142 (92.6%)	1135 (88.3%)	
2	78 (6.3%)	137 (10.7%)	
3	13 (1.1%)	12 (0.9%)	
4	0 (0%)	1 (0.07%)	

Note: *P-value was generated using a Wilcox Test

Number of complications number of segments resected decreased by 52% for less than three segments and 9% for more than three segments over time (p-value <.001). Multivariate analysis showed a significant relationship between number of segments resected and number of complications (slopes 1.78, p-value <.001) and number of severe complications (slopes 2.14, p-value <.001). Results for number of segments resected are shown in Table 15.

Table 15. *Results for Number of Segments*

Univariate Logistic Wound INF	Odds Ratio (95% CI)	p-value
> = 3 Segments	1.23 (0.78-1.92)	0.363
Univariate Logistic Int Abd Inf or Abc		
> = 3 Segments	1.78 (1.28-2.49)	0.001
Univariate Logistic 90D Mortality		
> = 3 Segments	7.74 (3.58-19.29)	<.001
Poisson Regression- Number of Complications	Slope/ Estimates	p-value
< 3 Segments	0.48	
> = 3 Segments	0.91	<.001
Poisson Regression- Number of Severe Complications		
< 3 Segments	0.16	
> = 3 Segments	0.37	<.001
Multivariate Analysis Number of Complications	Slopes	p-value
Number of Segments	1.78	<.001
Multivariate Analysis Number of Severe Complications		
Number of Segments	2.14	<.001

Finally, total amount of fluid was statistically significant in all univariate, Poisson and multivariate regressions. Results for total amount of fluids given are shown in Table 16.

Table 16. *Results for Total Amount of Fluids Given*

Univariate Logistic Wound INF	Odds Ratio (95% CI)	p-value
Total Amount of Fluids	1.02 (1.01-1.03)	0.007
Multivariate Logistic Wound INF		
Total Amount of Fluids	1.01 (1-1.02)	0.005
Univariate Logistic Int Abd Inf or Abc		
Total Amount of Fluids	1.02 (1.01-1.03)	<.001
Multivariate Logistic Int Abd Inf or Abc		
Total Amount of Fluids	1.02 (1.01-1.02)	<.001
Univariate Logistic 90D Mortality		
Total Amount of Fluids	1.03 (1.02-1.04)	<.001
Multivariate Logistic 90D Mortality		
Total Amount of Fluids	1.03 (1.02-1.04)	<.001
Poisson Regression- Number of Complications	Slope/ Estimates	p-value
Total Amount of Fluids	1.01	<.001
Multivariate Logistic Number of Complications		
Total Amount of Fluids	1.01	<.001
Poisson Regression- Number of Severe Complications		
Total Amount of Fluids	1.02	<.001

Multivariate Logistic Number of Severe Complications		
Total Amount of Fluids	1.02	<.001

Chapter Summary

Chapter four presented the results from the statistical analysis of this study in an effort to assess for a relationship between changes in anesthetic technique and outcomes for patients undergoing hepatic resection. The relationships with the use of a central venous catheter were analyzed using univariate, Poisson, and multivariate regression. The findings revealed that there was a univariate statistical significance associated between the presence of central venous catheter and 90-day mortality as well as number of severe complications. There was univariate significance suggesting patients who were extubated in the OR had more complications than those who were not. Use of morphine is associated with an increase in superficial wound infection as well as fewer number and severity of complications.

Additionally, the analyses incidentally demonstrated a relationship between gender, number of segments resected, and total amount of fluid given and outcomes.

Chapter five will present and discuss the research findings as they pertain to the study objectives. Additionally, the advantages and limitations of the study will be presented as well as any recommendations for future research.

Chapter 5: Discussion

Chapter five provides a summary of the study and an interpretation of the results described in Chapter Four.

Summary and Overview of the Problem

Central venous pressure (CVP) has traditionally been considered a valid measurement of fluid status. This measurement was incorporated into an anesthetic technique for patients undergoing hepatic resection at Memorial Sloan Cancer Center (MSKCC) in the mid 1990s in an effort to decrease blood loss. This technique which involved keeping the CVP at less than five mmHg until the specimen was removed, in concert with the surgeon's ability to control inflow into the liver, resulted in lower blood loss and a decrease in overall complications associated with this patient population at MSKCC. Starting in the early 2000s, published clinical research began to emerge questioning the validity and accuracy of CVP as a predictor of fluid status. In order to measure CVP, it is necessary to introduce a central venous catheter (CVC) in these patients. There are many complications associated with insertion of a CVC. In light of the findings that were increasingly being reported in the literature, the use of central venous catheters for the purpose of fluid management in was abandoned at MSKCC for patients undergoing hepatic resection. This change in anesthetic practice was one of three that occurred between 2007 and 2016. In addition to no longer introducing CVCs into patients for the purpose of fluid management, high doses of morphine were abandoned in favor of the more predictable effects of sublingual nitroglycerin. This allowed for early extubation of this patient population. Prior to this change, patients were extubated in the PACU hours after the procedure had ended. Finally, the use of dynamic measurements was gaining popularity around the same time the measurement of CVP was falling out of favor. From 2014 on, patients undergoing hepatic resection were being managed with the use of devices that allowed for dynamic measurement of fluid status, and therefore were treated with goal directed fluid therapy (GDFT). It is theorized that the evidence-based changes in the LCVP technique for patients undergoing hepatic resection at MSKCC lead to improved outcomes.

Purpose of the Study

The purpose of this study was to assess the relationship between changes in anesthetic technique over a 10-year period and outcomes in patients undergoing hepatic resection at MSKCC.

Review of Theory and Research Question

Avedus Donabedian (Donabedian, 1978) introduced what became a widely accepted theory that measured quality of healthcare in 1966. Donabedian described three constructs and their relationships; structure, process and outcome. First, he DEFINED quality. Donabedian concluded “Which of a multitude of possible dimensions and criteria are selected to define quality will, of course, have profound influence on the approaches and methods one employs in the assessment of medical care” (Donabedian, 2005). The development of the theory involved a need to assess what needed needed to be assessed in order to determine a level of quality. In doing so he settled on structure as defined by variables such as buildings, administrators, policies and staff, process as defined by variables where the healthcare is being delivered to the patient such as procedures and techniques, and finally outcomes as defined as variables such as complications and length of stay.

This study utilized two of Donabedian's constructs, process and outcomes. In this case the process is the use of CVC for the purposes of managing fluid status. That process, in theory, has a relationship with outcomes, in this case, in the form of manifestation of complications in this patient population at the institution where the care was rendered. The research question posed was: Is there a relationship between intraoperative insertion of CVC for the purpose of fluid management in hepatic resection and outcomes?

Methodology

A non-randomized, non-experimental, retrospective, cohort design was used to explore the possibility of relationships between the variables of insertion of CVC, use of morphine, and fluid management with GDFT. The hepatobiliary and anesthesia databases were queried for cases between January 1, 2007 and December 31, 2016. Descriptive statistics were used to characterize the variables and assess for relationships. Univariate, Poisson, and multivariate regression analyses were conducted to distinguish the magnitude and significance of those relationships.

Study Findings

Findings of the study were presented here regarding the hypothesis and research objectives. Theoretical and practical ramifications were justified as evidenced in the review of the literature. The study results suggest that there was an association between the presence of central venous catheter and 90-day mortality as well as severe complications. Multivariate analysis eliminated these relationships when all other significant finders were held constant. Use of morphine is associated with an increase in wound infection and, conversely, improved outcomes regarding number and severity of complications.

Additionally, the analyses incidentally demonstrated a relationship between gender, number of segments, and total fluids given and outcomes.

Hypotheses

Three of the four hypotheses were supported.

Hypothesis one (H_1)

Hypothesis one (H_1) assessed for a relationship between the use of central venous catheters and outcomes for patients undergoing hepatic resection.

- Hypothesis one (H_1): <u>There is a relationship between the use of central venous catheters and outcomes in patients undergoing hepatic resection.</u>

The findings suggest that presence of a CVC increases superficial, and deep wound infections. There is a significant link to 90day mortality with CVC, over three-fold. This can be explained by many things, not the least of which is that the cases with CVC beyond the change in practice may have been those that fall into a more complex category. It is also clear from the results that the incidence of complications have decreased over time.

Hypothesis two (H_2)

Hypothesis two (H_2) assessed for a relationship between the time of extubation and outcomes for patients undergoing hepatic resection.

- Hypothesis two (H_2): There is a relationship between the time of extubation and outcomes in patients undergoing hepatic resection.

Clinical significance here shows a decrease in superficial and deep wound infections. The apparent association with 90day mortality is notable and could possibly be explained by the fact that patients who remain intubated since the change in practice are those that have been through more complex procedures which are associated with poor outcomes. Significance regarding number of complications is underscored by the improvement over time in both extubated and not extubated patients. The findings suggest that not extubated patients tend to have fewer complications over all, but incidence of severe complications are at about the same in both groups.

Hypothesis three (H_3)

Hypothesis three (H_3) assessed for a relationship between the use of morphine for the purpose of LCVP and outcomes for patients undergoing hepatic resection.

- Hypothesis three (H_3): There is a relationship between the use of morphine for the purpose of LCVP and outcomes in patients undergoing hepatic resection.

The findings suggest that use of morphine is associated with superficial wound infections but not deep wound infections. This alone supports the change in practice to eliminate the use of morphine in favor of an alternative medication to lower CVP. The relationship between not using morphine and number of complications shows a larger percent of improvement for the time under investigation, 50% versus 22% in patients where morphine was used. Similarly, and also demonstrating significance was the relationship between not using morphine and severe complications. The gap between using morphine and not using morphine was much closer, which may be explained by overall decrease in severe complications over time. Additionally, the amount of morphine given was associated with fewer sever complications. It appears patients who received morphine have fewer complications as well as fewer severe complications than those who do not. This contradicts the association with superficial wound infections.

An incidental finding suggested a relationship between the female gender and outcomes. The results demonstrate that being female is associated with decreased incidence of wound infection, decreases chances for 90day mortality, decreased incidence of number of complications, and a decreased incidence of severe complications. Further analysis showed that women in the population being investigated had fewer co-morbidities than their male counterparts. It is also possible that women patients may have a separate primary cancer which generally means that the hepatic resection they may have had may have been less complex than those performed in male patients. This would explain a lower incidence of complications in this population.

The relationship described regarding the number of segments resected, and total amount of fluids given, and outcomes is in line with published evidence. Patients who have more complex procedures as well as those who receive more fluid tend to do worse than those who do not. This is the rationale behind exploration of alternative approaches to treatment of patients who would require multiple segments and the increasing popularity of fluid optimization through GDFT.

Contribution to the Literature

At this time, there are no studies that look specifically at the evolution of the LCVP technique and the potential relationships that may exists with outcomes in patients undergoing hepatic resection. Evidence based practice has evolved since the development of the LCVP technique. With the intention of improving outcomes, the use of morphine to lower the CVP during these cases was abandoned, thus allowing for an earlier extubation and therefore, in theory, improved outcomes due to the elimination of complications associated with prolonged intubation and positive pressure ventilation. Marik et al's (Marik P. & Cavallazzi R., 2013) contribution to the literature supported the utilization of dynamic measurements in favor of CVP and therefore the subsequent abandonment of the use of CVCs and their potential associated complications. These changes in practice and their support based on these findings will contribute to the ever-growing knowledge base providing evidence to improve practice in the patient population.

Theoretical Implications

Avedis Donabedian described a framework for assessing the quality of care. Donabedian used structure, process, and outcomes in his theory measuring the quality of healthcare (Donabedian, 1978). For the purpose of this dissertation, the constructs considered were process and outcomes. The variables were whether a CVC was inserted, patients were extubated in the OR, whether morphine was used, how the fluid status was managed (process) and incidence complications associated with major organs, the gastrointestinal system as well as infection, hemorrhage, wound breakdown and length of stay (outcome).

The change in practice the eliminated the use of CVCs in this patient population theoretically decreased the incidence of complications associated with CVCs. The results support this with the relationship between CVC and 90day mortality (OR 3.34, p-value <.001). There was also a significant relationship between the use of CVC and severe complications. Regarding use of CVC, it would appear that a change in process has improved outcomes.

The results regarding the extubation of patients in the OR are somewhat conflicting. Patients who were extubated reached statistical significance only in the number of complications category. The results suggest that patients who are extubated in the OR are slightly more likely to have any complication than those who were not extubated. These findings are in conflict with the clinically significant results that suggest extubating a patient in the OR is associated with improved outcomes over the time of the investigation.

The use of morphine was associate increased wound infections and any complications but a slight improvement regarding severe complications. These findings suggest that the change in practice was arguably supported and therefore in line with improved patient outcomes.

Donabedian thought that process had specific importance in measuring quality. In this case the quality is measured by complications associated with anesthetic practice in patients undergoing hepatic resection. Donabedian believed that focus should be on improving outcomes by way of improving process. However, not all improvements in process significantly affect the outcome (Harolds, 2015). What is supported in this investigation is that changes in process can have a relationship with outcomes but not all changes in process, even those ostensibly founded on evidence, will necessarily influence outcomes in the intended, or extent, intended.

Practical Implications

The results from this study have practical implications for anesthesia care providers who care for patients undergoing hepatic resection. The LCVP technique was developed to decrease blood loss in this patient population. The evidence showed that controlling CVP with the use of morphine during hepatic resection was a safe and effective practice (Cunningham et al., 1994; Melendez et al., 1998). With the innovation of new measurements for assessing fluid status, specifically SVV, SPV,PPV, and PVI and evidence in the literature that the measurement of CVP was no longer considered accurate, the LCVP technique was modified over time (Marik et al., 2008, 2009; Marik P. & Cavallazzi R., 2013; Frédéric Michard, 2005).

This current study demonstrated a significant relationship between presence of a CVC and 90day mortality and severe complications. Practice at MSKCC no longer involves using the CVP measurement for the LCVP technique in favor of use of dynamic measurements. The results from this study support this change in practice. The clinically significant findings suggest that presence of a CVC may be associated with increased wound infection, deep wound infection or abscess, 15% and 10% respectively. Presently at MSKCC, case complexity drives the decision to use or not use a CVC. One could argue that presence of the CVC is associated with poor outcomes due to the fact that these procedures tend to be more complicated, lose more blood and therefore are prone to complications (Kingham et al., 2015).
This may be the case with this population, however, avoiding the use of CVC when not necessary appears to be supported by the findings of this study.

Extubation of patients undergoing hepatic resection was associated with a clinically significant decrease in infections both superficial and deep wound or abscess. Overall complications over time decreased, which is a positive finding. However, it appears that early extubation does not show the same improvement in number of complications and is on par with severe complications with those patients that were not extubated. These findings support the hypothesis that there is a relationship, but not in the manner in which it was intended. The evidence in the literature supporting early extubation and limited mechanical ventilation may still take precedence over these findings (Nobili et al., 2012).

Use of morphine for the purpose of lowering the CVP shows a relationship with increase in superficial wound infections. However, the results from the Poisson regression suggest that the association between morphine and number of complications as well as severe complications improved over time, and not using morphine showed better results. The practice of using morphine not only fell out of favor for hepatic resections at MSKCC but was virtually eliminated from all practice unless a patient was allergic to the alternatives. The opioid it was replaced with, for the most part, was hydromorphone. Interestingly, at the time of this writing, there is a severe national shortage of hydromorphone and morphine has been restocked as the opioid of choice until such time that stocks of hydromorphone have been replenished. However, the indication for the use of morphine at this time is purely for analgesia.

Limitations

Disadvantages of a retrospective study design include limited control of the investigator over the approach to data gathering and the nature and quality of the baseline measurements. Additionally, it is difficult to account for input failures, various forms of bias, maturation and practice changes. The largest limitation of this investigation is that it is not possible to infer causality from the results. Additionally, the data was incomplete, sample size does impact the ability to address the research question(s) (Hully et al., 2013).

Threats to Internal Validity

"With quasi-experiments and correlational studies, there are competing explanations, which are sometimes called threats to internal validity"(Polit, 2006). Selection bias in an unavoidable threat to internal validity in retrospective study design. One could argue that patients undergoing hepatic resection are predisposed to unique categorical complications. If a population is inherently likely to demonstrate a characteristic, variables that influence these outcomes may be impossible to account for.

Historical threats are occurrence of events concurrent with variables under investigation that can affect the outcome (Polit, 2006). In this case, an example of a historical threat is a change in surgical technique or patient selection that may have had an influence on the outcomes that were being measured. If the surgeons improved their technique or eliminated a particular procedure due to higher risk of poor outcomes, this would have an effect on validity of the findings.

Retrospective study design necessitates the investigators inclusion of alternative explanations for the findings. Rival variables that were not included in the analysis cannot be excluded as potential confounders leading to the findings (Polit, 2006).

Threats to External Validity

"External validity concerns inferences about whether relationships found for study participants might hold true for different people, conditions, and settings"(Polit, 2006). The population under investigation is narrow, that is, patients undergoing hepatic resection. The practices at one institution may not necessarily be applicable to other those at other institutions. It is also not known, in this case, how many other institutions are practicing the same LCVP technique that was first described by Cunningham et al. (1991) and later validated as safe and effective by Melendez et al. (1998) (Cunningham et al., 1994; Melendez et al., 1998). It is also unknown to what degree, if any, the LCVP technique at other institutions has evolved in response to evidence in the literature. It is safe to say, only, that the findings reported in this investigation are applicable to the population investigated at the institution where the study was conducted.

Conclusions and Recommendations for Future Research

This investigation examined relationships between changes in anesthetic technique in patients undergoing hepatic resection and outcomes. The study revealed a relationship between presence of CVC and 90day mortality and presence of CVC and severe complications. Regarding extubation of the patient in the OR, there was a clinically significant association with decrease in infection rates and a mildly significant association between extubation in the OR and less protective effects when compared to extubation in the post anesthesia care unit. Use of morphine for the purposes of lowering the CVP fell out of favor during the time period being investigated. This study revealed that use of morphine for this purpose was associated with an increase in wound infection. There was also a relationship revealed between use of morphine and any complications. This relationship was also demonstrated with multivariate regression. Conversely, the use of morphine was associated with fewer severe complication, this may be explained by alternative approaches to LCVP technique in these cases.

In 2015, Kingham et al. (2015) attributed improvements in outcomes to better patient selection, improved surgical techniques and utilization of alternative therapies (Kingham et al., 2015). The purpose of this study was to assess whether changes in anesthesia practice over an updated timeframe would demonstrate a relationship with outcomes in the same patient population. Further study might take into account more variables or a narrower approach considering the wide spectrum of cases assessed here. Additionally, it would be interesting to know if the use of GDFT has a relationship with outcomes in the timeframe or going forward. It is possible that other variables associated with anesthetic technique may have influenced the results. Of note, the elimination of a number of cases due to missing data may have affected the findings. Going forward, research assessing the impact of anesthetic technique in this population should advance with more consistent data collection. At this time, at MSKCC all data is maintained electronically, as a result, prospective research will most certainly demonstrate improved internal and external validity.

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