Original Article

Prospective, Randomized Clinical Trial Comparing use of Intraoperative Transesophageal Echocardiography to Standard Care during Radical Cystectomy

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Abstract

Purpose: Our prospective, randomized clinical study aims to evaluate the utility of intraoperative transesophageal echocardiography (TEE) in patients undergoing radical cystectomy. **Materials and Methods:** Eighty patients were randomized to a standard of care group or the intervention group that received continuous intraoperative TEE. Data are presented as means ± standard deviations, median (25th percentile, 75th percentile), or numbers and percentages. Characteristics were compared between groups using independent sample *t*-tests, Wilcoxon–Mann–Whitney tests or Chi-square tests, as appropriate. All tests were two-sided and $P < 0.05$ was considered to indicate statistical significance. **Results:** Both groups had similar preoperative demographic characteristics. There was a significant difference between central line insertion with all insertions in the control group (15%, 6 vs. 0%, 0; $P < 0.003$). Of all the perioperative complications, 80% occurred in the control group versus 20% in the TEE group, with 21% of controls experiencing a cardiac or pulmonary complication compared to 5% in the TEE group (8 vs. 2, $P < 0.04$). The control group patients were more likely to have adverse cardiac complications than the TEE group (15%, 6 vs. 3%, 1; $P < 0.040$). Postoperative cardiac arrhythmia was observed only in the control group (13%, 5 vs. 0%, 0; $P < .007$). Prolonged intubation was only observed in the control group (10%, 4 vs. 0%, 0; $P < 0.017$). **Conclusion:** TEE can be a useful monitoring tool in patients undergoing radical cystectomy, limiting the use of central line insertion and potentially translating into earlier extubation and decreased postoperative cardiac morbidities.

Keywords: *Echocardiography, fluid therapy, radical cystectomy, transesophageal*

Introduction

Open radical cystectomy represents the most effective treatment for patients with muscle-invasive bladder cancer and is also a viable option for patients with high-grade, nonmuscle invasive disease. Open radical cystectomy can be a very challenging procedure, with published morbidity rates from experienced centers at 27%–45% and perioperative mortality rates at 3%.[1,2]

A major challenge in managing patients undergoing open radical cystectomy is maintaining intraoperative hemodynamic stability. A wide variety of factors contribute, including large blood loss, fluid shifts, inability to accurately assess urine output, and patient factors (preoperative cardiovascular disease/medications, diabetes, hypertension, obesity, and lung disease). Essentially, all patients receive invasive blood pressure monitoring and a substantial percentage of patients undergo central venous pressure (CVP) monitoring to aid intraoperative hemodynamic assessment. Even with such invasive monitoring, maintaining intraoperative hemodynamic stability is challenging and may lead to an increase in perioperative morbidity and mortality.[1]

Over the past 20 years, intraoperative transesophageal echocardiography (TEE) has revolutionized the perioperative care of patients undergoing cardiac surgery.[3] It allows direct, accurate assessment of intravascular volume and myocardial contractility, is considered useful in improving clinical outcomes, and the information obtained is better than that obtained from CVP monitoring.[4,5]

At present, no clinical study exists assessing the potential clinical benefits of intraoperative TEE in patients undergoing open radical cystectomy. Our prospective, randomized clinical study aims to evaluate

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the utility of intraoperative TEE in patients undergoing open radical cystectomy. We hypothesize that when compared to patients without TEE, patients randomized to receive this intraoperative monitoring will exhibit decreased use of invasive venous pressure monitoring, improved intraoperative fluid management, and decreased requirements for intravenous vasoactive medications, which may translate into decreased perioperative complications.

Materials and Methods

This clinical trial was approved by the institutional review board at our institution and registered at ClinicalTrials.gov (NCT03058250). Patients were enrolled into the study between 2012 and 2014. Written informed consent was obtained by the attending anesthesiologist on the morning of surgery from 80 patients undergoing elective radical cystectomy for invasive bladder cancer and patients were prospectively randomized into one of two groups, control and TEE. Previous clinical investigations have demonstrated that this number of patients will yield statistically significant differences between groups regarding important postoperative complications.[6] Patients were randomized by the statistician using a software program for computer generation of a simple random allocation sequence. Inclusion criteria were all adult (age >18), hemodynamically stable patients undergoing elective radical cystectomy. Exclusion criteria were patient refusal, emergent surgery, preoperative mechanical ventilation, preoperative hemodynamic instability, and esophageal or gastric pathology contraindicating insertion of the TEE probe. If inclusion criteria were met, patients were consented on the day of surgery. All patients, in both the control and TEE group, received a standardized general anesthetic with radial artery blood pressure monitoring, with the goal of tracheal extubation in the operating room immediately following surgery. Anesthetic technique in both groups was standardized to intravenous midazolam, fentanyl, propofol, hydromorphone, vecuronium, and inhaled desflurane in amounts appropriate for intraoperative tracheal extubation. Hemodynamic support for hypotension was standardized to intravenous ephedrine or phenylephrine as first-line agents, at the discretion of the anesthesiologist, followed by other vasopressors (vasopressin and epinephrine) if necessary. In the control group, the attending anesthesiologist was a general anesthesiologist. While TEE was not routinely used in this group, it was allowed if requested by the general anesthesiologist during the intraoperative period in a "rescue" role to evaluate life-threatening hemodynamic instability. Patients in the TEE group had TEE used throughout the intraoperative period to assist with fluid and hemodynamic management. The probe was removed before extubation. The attending anesthesiologist in this group was a cardiac anesthesiologist who had passed the National Board of Echocardiography's Examination of Special Competence in Perioperative TEE.

Primary endpoints were intraoperative fluid balance and vasoactive medication use. Secondary endpoints were central line insertion, return of bowel function, tracheal extubation time, postoperative morbidities (pulmonary and cardiac), Intensive Care Unit (ICU) admission, hospital length of stay, and mortality.

Statistical analysis

We calculated the minimum number of participants required to achieve 80% power at a Bonferroni-adjusted 0.05 significance level using data from a similar study by Pillai *et al*.[6] All analyses were performed using JMP, version 13, (SAS Institute, Cary, NC, USA). Data are presented as means ± standard deviations, median (25^{th} percentile, 75^{th} percentile) or numbers, and percentages depending on the variable type and distribution. Characteristics were compared between groups using independent sample *t*-tests, Wilcoxon–Mann–Whitney tests, or Chi-square tests, as appropriate. All tests were two-sided and $P < 0.05$ was considered to indicate statistical significance.

Results

Of the 80 patients consented and randomized for the study, 77 had complete data acquisition in the control group (39) and TEE group (38). One patient was lost in the control group due to inadequate intraoperative data collection and inability to insert an arterial line. Two patients were lost in TEE group due to inability to insert a TEE probe and inadequate intraoperative data collection.

There were no significant differences in preoperative demographic factors and comorbid conditions between the two groups [Table 1] except more frequent use of statin medications in the TEE group (31%, 12 vs. 58%, 22; $P < 0.016$). Cardiac, pulmonary, and renal diseases were similarly represented between the two groups. The revised cardiac risk index score was assessed to predict major cardiac complications following elective noncardiac surgery in this population, and it was similar in both groups [Appendix A]. All patients received a minimum score of 1 due to high-risk surgery.

In both groups, experience of the secondary provider assigned to the case did not differ significantly [Table 2] with residents and nurse anesthetists equally represented between the two groups. Operating room time and length of surgery were similar between the two groups. There was a significant difference between central line insertion for CVP monitoring, with all central line insertions in the control group and none in the TEE group (15%, 6 vs. 0%, 0; $P < 0.003$). All central line insertions were planned and placed before start of surgery and inserted for the purposes of extra monitoring. There were no statistical differences in intraoperative total blood loss, total intraoperative fluid administration, and transfusion. There were no significant differences with regard to intraoperative vasopressor use in either group.

Table 1: Patient characteristics

	Control (*n*=39) (%)	TEE (*n*=38) (%)	*P*
Age (year)	68±10	66±9	0.242
Sex			
Male	28 (72)	30 (77)	0.598
Female	11 (28)	8 (21)	
BMI (kg/m^2)	30±12	29±5	0.402
ASA	3	3	>0.999
Revised cardiac risk index score	1.6±0.9	1.7±0.7	0.823
History of smoking	34 (87)	31 (82)	0.497
Hypertension	29 (74)	23 (61)	0.193
Diabetes	12 (31)	13 (34)	0.747
Coronary artery disease	10 (26)	10 (26)	0.946
CHF	4 (10)	8 (21)	0.188
COPD	12 (31)	10 (26)	0.665
B-blocker	15 (38)	11 (29)	0.376
Calcium channel blocker	12 (31)	8 (21)	0.329
ACE inhibitor	11 (28)	17 (44)	0.130
Diuretics	12 (31)	7 (18)	0.206
Statins	12 (31)	22 (58)	0.016*
Nitrates	2 (5)	1 (3)	0.567
Oral hypoglycemic	6 (16)	8 (21)	0.553
Insulin	3 (8)	3 (8)	>0.999
Bronchodilator	6 (15)	5 (13)	0.780
Preoperative serum creatinine (mg/dl)	1.3	1.1	0.219

*<0.05 is significant. Data are presented as mean±SD, or absolute value (%). Diabetes defined as treatment with oral hypoglycemic or insulin. TEE: Transesophageal echocardiography, BMI: Body mass index, ASA: American society of anesthesiologists, ACE: Angiotensin-converting enzyme, COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, CHF: Congestive heart failure

Table 2: Intraoperative data

	Control (*n*=39) (%)	TEE (*n*=38) (%)	*P*
Provider for case			
CRNA	6 (15)	5 (13)	0.927
CA1	20 (51)	21 (55)	
CA2	9 (23)	7 (18)	
CA3	4 (10)	5 (13)	
Operating room time (min)	305±101	299±63	0.761
Surgery time (min)	240±83	226±56	0.462
Central venous line insertion (*n*)	6 (15)	0	0.003*
EBL (ml)	1116±951	987±433	0.447
Intraoperative fluids administered (ml)			
Crystalloid	4147±1595	3732±1080	0.185
Colloid	615±640	638±437	0.855
Intraoperative transfusion (units)			
PRBC	1.8±3.4	0.7±0.9	0.082
FFP/platelets	0.5±1.9	0.05±0.3	0.096
Vasopressor administered (*n*)			
Ephedrine	32 (82)	30 (79)	0.730
Phenylephrine	25 (64)	26 (68)	0.688
Other	7 (18)	3 (8)	0.183

*<0.05 is significant. Data are presented as mean±SD, or absolute value (%). Other vasopressors used were vasopressin and epinephrine. SD: Standard deviation, TEE: Transesophageal echocardiography, CRNA: Certified registered nurse anesthetist, CA1: Clinical anesthesia 1st year, CA2: Clinical anesthesia 2nd year, CA3: Clinical anesthesia 3rd year, EBL: Estimated blood loss, PRBC: Packed red blood cell, FFP: Fresh frozen plasma

Myocardial ischemia, new-onset cardiac arrhythmia, respiratory failure, and respiratory distress resulting in reintubation or pulmonary edema that occurred intraoperatively or postoperatively during the hospital stay were all considered to be adverse perioperative events. Of all perioperative complications, 80% occurred in the control group versus 20% in the TEE group, with 21% of controls experiencing a cardiac or pulmonary complication compared to 5% in the TEE group (8 vs. 2, $P < 0.04$) [Table 3]. Stratifying perioperative complications revealed that the control group patients were more likely to have adverse cardiac complications than the TEE group (15%, 6 vs. 3%, 1; $P < 0.040$). The incidence of myocardial ischemia was the same in both groups (1 patient in each group), but postoperative cardiac arrhythmia was observed only in the control group (13%, 5 vs. 0%, 0; $P < .007$). No difference was observed among respiratory complications (8%, 3 vs. 3%, 1; $P < 0.30$).

Prolonged intubation was defined as remaining intubated after the completion of surgery. Prolonged intubation was only observed in the control group (10%, 4 vs. 0%, 0; $P < 0.017$). Although patients in the control group had more ICU admissions, this did not reach statistical significance (18%, 7 vs. 8%, 3; $P < 0.183$). There were no differences in the mean number of postoperative days until initial oral intake (4 vs. 5; $P < 0.448$), return of bowel function (4 vs. 4; $P < 0.890$), and duration of hospital stay (10 vs. 8; $P < 0.128$) between the two groups. There was one death in the control group (1 vs. 0; $P < 0.241$). The patient had 4 l of surgical blood loss, was transfused 15 units of packed red blood cells (PRBCs), had postoperative kidney and respiratory failure, and died on the postoperative day 19.

Discussion

This prospective, randomized clinical trial found that intraoperative TEE, when compared to the standard of care, was significantly associated with decreased central line insertion, decreased prolonged intubation, and decreased perioperative cardiac arrhythmia. Perioperative complications ranged from pulmonary edema causing respiratory distress to non-ST elevated myocardial infarction requiring coronary artery stent placement. Of all the perioperative complications, 80% occurred in the control group. Postoperative cardiac arrhythmias were only observed in the control group. Four patients had atrial fibrillation with rapid ventricular rate and one patient

Table 3: Postoperative outcomes

	Control (*n*=39) (%)	TEE (*n*=38) (%)	*P*
Perioperative complications	8 (21)[H]	2 (5)	0.040*
Cardiac	6 (15)	1 (3)	0.041*
Myocardial ischemia	1 (3)	1 (3)	0.985
Cardiac arrhythmia	5 (13)	0	0.007*
Pulmonary	3 (8)	1 (3)[t]	0.306
Re-intubation	1 (3)	1 (3)	0.985
Pulmonary edema	2 (5)	1 (3)	0.567
Prolonged intubation	4 (10)	0	0.017*
ICU admission	7 (18)	3 (8)	0.183
Initial PO intake (POD)	4±2	5±2	0.448
Return of bowel function (POD)	4±2	4±2	0.890
Length of hospital stay (days)	10±8	8±4	0.128
Death (*n*)	1 (3)	0	0.241
	Acute kidney failure requiring hemodialysis, respiratory failure and sepsis		

*<0.05 is significant. Data are presented as mean±SD or absolute value (%). Data reported as mean±SD was compared using the unpaired *t*-test, and data reported as number of patients (%) were compared using Pearson Chi-square test. Myocardial ischemia defined by new ST changes and elevated cardiac markers of injury. Cardiac arrhythmia defined as new onset atrial/ventricular arrhythmia documented on EKG, requiring medication/cardiology intervention. Pulmonary edema defined as new onset edema resulting in clinical symptoms (desaturation, labored breathing) documented on CXR requiring medication and/or supportive care. Prolonged intubation defined as the number of patients that remained intubated after the completion of surgery. [H]One patient had both cardiac and pulmonary complications and is listed in both groups, [t]This patient had pulmonary edema and was re-intubated and is listed in both groups. SD: Standard deviation, TEE: Transesophageal echocardiography, ICU: Intensive Care Unit, POD: Postoperative day, EKG: Electrocardiogram, CXR: Chest X-ray

experienced bradycardia with first-degree atrioventricular block. New-onset cardiac arrhythmias affect about 7% of patients after noncardiac surgery, with atrial fibrillation being the most common.[7] Attenuation of the stress response during surgery may decrease postoperative cardiac irritability.

Perioperative fluid management remains challenging and is an abundantly represented topic in the anesthesia and surgery literature.[8-16] Goal-directed treatment (GDT) may lead to fewer complications versus liberal administration of fluid. The term GDT encompasses several varying hemodynamic parameters with an underlying theme of patient specificity to optimize forward flow and perfusion. There is no unifying monitoring modality used in these studies, which range from pulmonary artery catheters to esophageal Doppler (EDM). Although TEE has not been utilized for the purpose of GDT, it provides patient-specific flow directed information such as preload, contractility, and cardiac output. Although there was no difference in total fluids between the two groups, volume administration for cardiac output optimization occurs throughout the surgical case, and total numbers do not reflect variability in administration. Similarly, Goepfert *et al*. did not find a difference in overall fluid balance or transfusion requirement but found a decrease in postoperative complications in a randomized controlled trial on cardiac surgery patients.[17] The authors concluded that therapeutic intervention based on the cardiac index and end-diastolic volume index is associated with improved end-organ function. In the absence of significant differences in total volume of administered fluid between the treatment and control group, other studies have also found a decrease in postoperative complications with the use of EDM.[18,19] Intraoperative EDM-guided fluid therapy has been shown to increase stroke volume, cardiac output, and oxygen delivery when compared to CVP, resulting in a decrease in postoperative complications.[20] In a meta-analysis, Hamilton *et al*. demonstrated that preemptive hemodynamic monitoring and targeted therapy reduced postoperative morbidity and mortality.[21] The use of intraoperative TEE correlates with these findings, in that better intraoperative monitoring allows targeted intervention throughout the case, likely attenuating large hemodynamic fluctuations. TEE may allow quicker identification of volume depletion and changes in contractility, resulting in immediate management. Ghaferi *et al*., using data from the American College of Surgeons National Surgical Quality Improvement Program from 2005 to 2007, concluded that complication rates decrease with early recognition and treatment.[22] The noted difference in cardiac complications can likely be attributed to utilization of TEE for timely volume optimization. A meta-analysis of randomized controlled studies by Kern and Shoemaker addressed clinical outcomes in critically ill patients after resuscitation.[23] They reviewed 21 trials and concluded decreased mortality in patients who received early treatment and therapy aimed at optimizing oxygen delivery. Especially, they stated that monitoring aimed at increasing the cardiac index improved outcomes. Interpretation of continuous volumetric and functional data provided by TEE assists with intraoperative optimization of cardiac output.

Several large studies have discredited CVP monitoring as useful for clinical decision making for fluid administration.[24-28] Right atrial pressure does not correlate with volume responsiveness or cardiac output. Despite the abundance of evidence against static CVP monitoring, many clinicians continue to use it to guide therapy.[29] Pulse pressure variation has gained traction since 2000 as a reliable measure of fluid responsiveness; however, it is accurate only in patients on mechanical ventilation with large tidal volumes (>8 ml/kg) and without arrhythmia and does not improve patient outcome.[30-32]

Venous access for volume resuscitation and monitoring of volume status were the reasons cited by providers for central line insertion in the control group, although all patients had standard peripheral intravenous access. Providers in the intraoperative TEE group were able to rely on echocardiography for monitoring of volume status and were not compelled to place a central line for additional venous access. There is a multitude of immediate and delayed complications associated with central venous access ranging from 4% to 7%.[33] Hemorrhage, stroke, and life-threatening complications have been reported with inadvertent arterial puncture and trauma to surrounding tissues. Ultrasound guidance decreases but does not eliminate the risk of mechanical injury.[34] Alternatively, TEE probe insertion and examination is associated with a very low risk of complications (0.2%–0.5%).[35] Minimal skill is required for probe insertion and knowledge on performing a basic TEE examination can be readily achieved by any provider. Volume assessment and myocardial contractility assessment can be achieved in the mid-esophageal four-chamber view and transgastric short-axis view. In this study, TEE provided a good alternative to central line insertion for monitoring of volume status.

Previous studies have indicated that fluid optimization using EDM improved return of gastrointestinal function, decreased length of stay, and improved oral intake.[6] Improvements in postoperative markers of gastrointestinal function were directly correlated to increased fluid administration. Our study did not find a significant difference in postoperative gastrointestinal outcomes, which may be due to no differences between the two groups with regard to mean intraoperative fluid administration.

Three out of the four patients with prolonged intubation had 4000 ml of blood loss and received 10, 15, and 12 units of PRBC's, respectively, and were taken to the ICU intubated. The fourth patient had 2000 ml of blood loss but received 10.5 L of intraoperative crystalloid and colloid and was subsequently taken to the ICU intubated. Although there was no statistical significance between mean blood loss between the TEE and control group, no patients in the TEE group had blood loss over 1850 ml. Thus, the increase in prolonged intubation in the control group can likely be attributed to large fluid shifts in 3 out the 4 patients due to blood loss. The fourth patient received fluids in excess of fluid loss and may have benefited from the intraoperative assessment of volume through TEE, which may have led to better optimization of administered fluid.

One of the limitations of this study is that only cardiac anesthesiologists certified in TEE were attending physicians for patients in the TEE group. Results of the study may have been effected by choice of anesthesiologist, with cardiac anesthesiologists potentially having increased expertise in managing complex patients.[36] However, given that intraoperative fluid management and vasopressor use was similar between the two groups it is unlikely that patient management styles varied greatly between cardiac and noncardiac anesthesiologists. Rather intraoperative decision-making about timing of fluids and vasopressors based on TEE monitoring, resulted in reduced fluctuations and extremes of hemodynamics, and translated into better outcomes for patients.[37] There was no difference between the control and TEE group among the secondary anesthesia providers. Basic TEE skills to ascertain information on preload and contractility can be attained with minimal training and do not require advanced fellowship training.[38] In addition, providers experienced in TEE can train others in the practice group on basic skills.[39]

Conclusion

TEE can be a useful monitoring tool in patients with multiple comorbidities undergoing complex surgical procedures with anticipated large blood loss, primarily serving to limit the use of central line insertion and potentially translating into decreased postoperative cardiac morbidities.

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Conflicts of interest

There are no conflicts of interest.

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Appendix

Appendix A: Revised cardiac risk index score		
History of MI?	Yes	No
MI <6 months?	Yes	No
Current angina?	Yes	No
History of ischemia evaluation?	Yes	No
Current nitroglycerine use?	Yes	No
History of CHF?	Yes	No
History of pulmonary edema?	Yes	No
History of valvular heart disease?	Yes	No
History of cerebrovascular disease?	Yes	No
Use of insulin?	Yes	No
Preoperative rales/S3?	Yes	No
Preoperative abnormal EKG rhythm?	Yes	No
Preoperative Q waves?	Yes	No
Preoperative CXR cardiomegaly?	Yes	No
Serum creatinine >2.0 mg/dl?	Yes	No
Poor general medical status	Yes	No
Ischemic heart disease?	Yes	No
CHF?	Yes	No

MI: Myocardial infarction, CHF: Congestive heart failure, CXR: Chest X-ray, EKG: Electrocardiogram