A Double-Blinded Randomized Trial to Compare the Effectiveness of Minimally Invasive Procedures Using Patient-Reported Outcomes

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BACKGROUND: The Institute of Medicine has included the comparison of minimally invasive surgical techniques in its research agenda. This study seeks to evaluate a model for the comparison of minimally invasive procedures using patient-reported outcomes.

STUDY DESIGN: A double-blinded randomized controlled trial (NCT01489436) was conducted. Baseline data were obtained, standardized anesthesia was induced, and patients were randomized to single-port (SP) or 4-port (FP) laparoscopic cholecystectomy. Perioperative care was standardized. The outcomes were pain (Visual Analog Scale) on postoperative day 1 (primary) and quality of life (Patient-Reported Outcomes Measures Information System and Linear Analog Self-Assessment), serum cytokines, and heart rate variability (secondary). Analysis was intention to treat. Using identical occlusive dressings, patients and the outcomes assessor remained blinded until postoperative day 2.

RESULTS: Fifty-five patients were randomized to each arm. There was no difference in demographics. Visual Analog Scale pain score on postoperative day 1 was significantly different from baseline in each group (SP: 1.6 ± 1.9 to 4.2 ± 2.4 vs FP: 1.8 ± 2.3 to 4.2 ± 2.2), but not different from each other ($p = 0.83$). Patients in the FP arm reported significantly less fatigue on postoperative day 7 than patients in the SP group (3.1 ± 2.1 vs 4.2 ± 2.2; $p = 0.009$). Fewer patients in the FP group required postoperative oral narcotics before discharge (40% vs 60%; $p = 0.056$). Cytokines levels and heart rate variability were similar between arms. In patients followed for >1 year, no difference in umbilical hernia rates was noted.

CONCLUSIONS: Early postoperative quality of life data captured differences in fatigue, indicating improved recovery after FP within a controlled trial. Physiologic measures were similar, suggesting that the differences between SP and FP are minimal. (J Am Coll Surg 2015;221:111−121. © 2015 by the American College of Surgeons)

Patients expect efficient medical care with minimal invasiveness and fast recovery.[1] The Institute of Medicine has included the comparison of minimally invasive surgical techniques in its research agenda. This supports the assumption that a comparative effectiveness investigation of minimally invasive surgical procedures might, in the future, serve as an important tool in the design of health care delivery. This study sought to evaluate a model for the comparison of minimally invasive procedures, using the example of single-port (SP) and 4-port (FP) laparoscopic cholecystectomy.

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Abbreviations and Acronyms

FP	= 4-port
HF	= high frequency
IL	= interleukin
LASA	= Linear Analog Self-Assessment
LF	= low frequency
PRO	= patient-reported outcomes
PROMIS	= Patient-Reported Outcomes Measures Information System
QOL	= quality of life
SP	= single port
T-score	= total score
VAS	= Visual Analog Scale

Patient morbidity and mortality after minimally invasive outpatient procedures such as cholecystectomy are generally <7%. These traditional outcomes measures have limited use as procedure comparators. A number of studies have taken patient-reported outcomes (PRO), such as quality of life (QOL) into account. Patient-reported outcomes measures have generated considerable interest at the NIH, where a Patient-Reported Outcomes Measures Information System (PROMIS) and, within this system, PROMIS-10, a short global assessment of QOL containing 10 questions, have been developed.[2] The PROMIS system items are more sensitive to change compared with legacy instruments, such as the SF-36.[3] Recent research in PRO has also yielded the validated Linear Analog Self-Assessment (LASA) tool, a single-item tool that can be used at the bedside. We have previously used both tools and found them responsive to perioperative changes in patients after laparoscopic surgery.[4,5] Several studies have compared SP and FP laparoscopic cholecystectomy previously, including using PRO. However, most studies were small, often underpowered, and did not account for confounders or did not collect preoperative baseline PRO data, making interpretation of the results difficult.[6,7]

To overcome the limitations of traditional outcomes measures, some investigators have used biomarkers to compare surgical procedures. Each skin incision generates pain and a neutrophil-mediated immune response with systemic consequences. Leung and colleagues[8] demonstrated significant differences in interleukin (IL) 1b and IL6 serum levels between patients undergoing laparoscopic vs open colectomy. The proinflammatory cytokine profile of patients in the laparoscopic group demonstrated significantly fewer increases than in the open group. Sarli and colleagues[9] demonstrated that smaller laparoscopic trocar incisions led to significantly less pain and analgesic use within the first 24 hours postoperatively. Other studies have not been able to consistently confirm similar differences between groups. Contributing factors for the different reporting are variabilities in specimen procurement and the lack of attention to the influence of sex, age, and circadian rhythms on circulating cytokine levels. A recent study with highly variable specimen procurement (±24 hours) demonstrated differences in IL6 serum levels between SP and FP cholecystectomy, although statistical significance was not reached with the small sample ($n = 35$; $p = 0.06$).[10]

Another tool to measure stress response in otherwise healthy individuals is heart rate variability.[11] Bickel and colleagues[12] have used the ratio of high-frequency (HF) bands and low-frequency (LF) bands to compare the physiologic impact of variations in abdominal pressure of patients undergoing laparoscopic cholecystectomy under general anesthesia. His group was also able to show that the type of gas used for insufflation (helium vs CO_2) changed the pattern of HF/LF ratio in an otherwise healthy patient cohort, clinically representing the increased peritoneal and systemic acidosis with CO_2 pneumoperitoneum compared with helium.[13] Our randomized trial aimed to standardize perioperative care and control for age, sex, circadian rhythm, and comorbidities, and used a rigorous and validated set of early patient-reported, biologic, and physiologic measures to compare 2 minimally invasive approaches with each other. We hypothesized that PRO would be able to detect clinically relevant differences between 2 minimally invasive surgical procedures.

METHODS

Informed consent was obtained for this IRB-approved study (NCT01489436) by a study coordinator blinded to the intervention.

Inclusion criteria were patients scheduled to undergo elective cholecystectomy for symptomatic gallbladder disease at a single center between August 2011 and February 2014. The center performs about 500 laparoscopic cholecystectomy procedures per year, two-thirds of them for elective indications. Exclusion criteria for the study were age younger than 18 years, pregnancy, American Society of Anesthesiologists class >3, chronic narcotic pain medication, autoimmune disease or immune-modulating therapy, gallbladder cancer, and suspected acute cholecystitis. Patients who could not provide consent for the study or were not willing to participate in the study were also excluded.

After patient enrollment, baseline measurements were obtained, including demographics, Visual Analog Scale (VAS), LASA and PROMIS-10 data, and cytokine levels (Table 1).