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Analgesic and Antiemetic Requirements After Minimally Invasive Surgery for Early Cervical Cancer: A Comparison Between Laparoscopy and Robotic Surgery

Pamela T. Soliman, MD, MPH[1], Ginger Langley, PharmD[2], Mark F. Munsell, MS[3], Hemang A. Vaniya, MD[1], Michael Frumovitz, MD, MPH[1], and Pedro T. Ramirez, MD[1]

[1]Department of Gynecologic Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Division of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX

ABSTRACT

Background. Women with early cervical cancer undergoing radical hysterectomy via minimally invasive surgery (MIS) have decreased blood loss and a shorter hospital stay compared with laparotomy. It remains unclear whether there is a difference in benefit to the patient between robotic surgery and traditional laparoscopy. We sought to compare postoperative analgesic and antiemetic requirements between the two approaches.

Methods. After institutional review board approval, the medication administration records of all patients who underwent MIS radical hysterectomy for cervical cancer at MD Anderson Cancer Center were reviewed. Analgesic and antiemetic medication use as well as visual pain scores was recorded. Descriptive statistics and nonparametric tests were used to compare the groups undergoing laparoscopy (LRH) and robotic surgery (RRH).

Results. A total of 85 patients underwent MIS for early cervical cancer, 55 LRH and 30 RRH. Median age was older in the RRH (42 vs. 52 years, $p = 0.001$). There was no difference in median body mass index (26.9 vs. 26.8 kg/m^2, $p = 0.71$). Length of stay was significantly shorter in the RRH (2 vs. 1 day, $p = 0.005$). Total intravenous opioids administered were significantly higher in the LRH (26.7 mg morphine equivalents) compared with the RRH (10.7 mg morphine equivalents) ($p = 0.001$). There was no difference in visual pain scores or antiemetics given.

Conclusions. Intravenous opioids administered were significantly less for RRH compared to LRH; however, there was no difference in visual pain scores. Prospective studies are being performed to evaluate quality of life in patients undergoing MIS for gynecologic cancers.

Total laparoscopic radical hysterectomy (LRH) was first reported in the early 1990s.[1,2] Since that time, there have been a number of single institution reports on the feasibility of laparoscopic radical hysterectomy and pelvic lymph node dissection in the treatment of early stage cervical cancer.[3–6] Robotic-assisted radical hysterectomy (RRH), an alternative minimally invasive approach to this procedure was first described in 2006.[7] Several studies confirming the safety and feasibility of this approach have also been published.[8–12] These studies have shown the benefit of minimally invasive surgery, both LRH and RRH, over laparotomy in regard to decrease in blood loss, shorter hospital stay, and shorter recovery time.[13]

To date, all of the studies evaluating the role of MIS in the treatment of early cervical cancer have focused primarily on surgical outcomes. Although MIS surgical approaches have consistently shown significant benefit over traditional laparotomy, it is unclear at this time whether there is a difference in benefit when comparing different minimally invasive surgical approaches. A recent study comparing single-port and conventional laparoscopic vaginal hysterectomy for benign indications found that postoperative pain and analgesic use was significantly lower in the single-port group.[14] This was the first study to

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P. T. Soliman, MD, MPH
e-mail: psoliman@mdanderson.org

suggest that different MIS approaches to surgery may have different benefits to the patient. Additional studies need to be performed to determine whether this difference in MIS approach is applicable to other clinical scenarios. The purpose of our study was to compare postoperative analgesic and antiemetic use during hospitalization between patients that underwent RRH and LRH for the treatment of early cervical cancer.

MATERIALS AND METHODS

With approval from our institutional review board, a retrospective review of all women who underwent a minimally invasive radical hysterectomy with pelvic lymph node dissection for the treatment of early stage cervical cancer by the Department of Gynecologic Oncology and Reproductive Medicine at MD Anderson Cancer Center was performed. This included procedures performed at MD Anderson Cancer Center's main hospital and those performed at St. Luke's Episcopal Hospital, where our surgeons operate. LRH was first offered at our institution in 2004, and from 2007 to 2010 both LRH and RRH were offered on the basis of surgeon preference. In order to account for any difference in practice during the different time periods, the LRH group was subdivided into surgical time periods: 2004–2006 and 2007–2010. Each subgroup and the entire LRH group were compared to RRH. Data collection included demographic characteristics, surgical information, and length of hospital stay.

The medication administration records were reviewed for each patient and the type and dose of each analgesic and antiemetic medication were recorded. Although it is standard practice within our group to write all postoperative pain and antiemetic medications as "prn" orders after MIS procedures, the type of medication used was at the discretion of the primary surgeon. In order to allow for comparison, all intravenous opioid doses were converted to morphine-equivalent doses based on standard conversions.[15] For example, 1.5 mg IV hydromorphone was equivalent to 10 mg IV morphine. For the antiemetics, several different agents were used. To allow for comparison, ondansetron 8 mg IV, prochlorperazine 10 mg IV, and promethazine 25 mg IV were all considered one dose of antiemetic therapy. The total number of doses administered during the hospital stay was recorded.

Visual pain scores (0–10), part of routine vital sign monitoring, were collected from the medical record at various time points. These were defined as "baseline" at their initial outpatient clinic visit, "preoperative" just before surgery, "postoperative" during the first set of vital signs measured after the procedure was completed, "discharge" the last set of vitals recorded before discharge from the hospital, and "follow-up" at their 4- to 6-week postoperative outpatient visit.

Fisher's exact test was used to compare LRH and RRH groups with respect to clinical stage and histology. The Wilcoxon rank sum test was used to compare LRH and RRH groups with respect to median age, medication use, and pain scores. Two-tailed tests were used with p values less than 0.05 considered statistically significant. All statistical analyses were performed by SAS 9.1 for Windows (SAS, Cary, NC).

RESULTS

Between April 2004 and August 2010, a total of 85 patients underwent a MIS radical hysterectomy and pelvic lymph node dissection for the treatment of early cervical cancer. Fifty-five procedures were performed with traditional laparoscopy and 30 by the robotic approach. The demographic characteristics are listed in Table 1. The median age was higher among women who underwent RRH compared to LRH (52 vs. 42 years, $p = 0.001$). There was no difference in median body mass index (BMI) between the groups (26.9 vs. 26.8 kg/m^2, $p = 0.71$). Length of hospital stay was statistically shorter in the RRH group (2 vs. 1 day, $p = 0.005$). There was no difference in stage ($p = 0.59$) or histologic subtype ($p = 0.24$) between the two groups.

The total IV analgesic and antiemetic medication doses administered during the hospitalization are listed in Table 2. The median total morphine equivalent IV dose was significantly higher in the LRH group (26.7 mg) compared to the RRH group (10.7 mg, $p = 0.003$). This finding was also seen when comparing RRH to each of the LRH subgroups; LRH 2004–2006 (28 mg, $p = 0.0024$) and LRH 2007–2010 (26.2 mg, $p = 0.0127$). In order to account for the difference in length of hospital stay between the LRH and RRH, we also calculated the morphine equivalent IV dose per hospital day utilized. There continued to be a significant difference in median IV analgesic use between the LRH (15.7 mg/day) and the RRH (9.5 mg/day, $p = 0.017$). In addition to IV opioids, 19 (31 %) of 55 in the LRH patients received 30–210 mg (median 90 mg) IV ketorolac during their hospital stay. In the RRH group, 6 (20 %) of 30 received 15–180 mg (median 60 mg) IV ketorolac during their hospital stay. This difference was not statistically significant ($p = 0.21$). There was no difference in the total IV antiemetic use between the two groups ($p = 0.72$).

Median pain scores were available for 76 patients during defined time points and are compared in Table 3. There was no difference in reported pain scores at baseline, preoperative, postoperative, at the time of hospital

TABLE 1 Demographic characteristics

Characteristic	Laparoscopy ($n = 55$)	Robotic ($n = 30$)	p
Age (years)			
Median	41.6	52.1	0.001
Range	25.6–63.6	27.9–75.9	
BMI			
Median (kg/m^2)	26.9	26.8	0.71
Range	18.0–47.3	20.3–38.1	
Length of stay (days)			
Median	2	1	0.005
Range	1–5	1–3	
Cervix stage, *n* (%)			0.59
IA1	3 (5 %)	4 (13 %)	
IA2	12 (22 %)	6 (20 %)	
IB1	37 (67 %)	19 (63 %)	
IB2	1 (2 %)	1 (3 %)	
Unknown	2 (4 %)	0	
Histology, *n* (%)			
Squamous	25 (45 %)	15 (50 %)	0.24
Adenocarcinoma	25 (45 %)	8 (27 %)	
Adenosquamous	3 (6 %)	3 (10 %)	
Clear cell	1 (2 %)	2 (7 %)	
Other	1 (2 %)	2 (7 %)	

discharge, or at the postoperative outpatient follow-up visit. Findings were similar when the LRH group was evaluated during each time period. We also calculated the change in pain score between baseline to postoperative, and baseline to discharge but there was no difference between the surgical approaches.

DISCUSSION

With the emergence of new technology and growing options for the approach to surgery, there are a number of factors that need to be considered when deciding the best surgical approach, including measures of quality of life. The purpose of this hypothesis-generating study was to determine whether there is a difference in postoperative opioid and antiemetic requirements in women who underwent LRH versus RRH. We chose to evaluate postoperative pain and nausea as these are factors that contribute to quality of life after surgery and can be evaluated to some extent in a retrospective manner. In our series of 85 consecutive MIS radical hysterectomy cases, we found that the total dose of IV opioids administered during the hospital stay was significantly lower in the RRH group compared to the LRH group, despite the patients in the RRH cohort being significantly older. In addition, the RRH patients had a significantly shorter hospital stay. This shorter stay, however, did not account for the difference in IV opioids administered. This is one of the first published series in gynecologic oncology looking at postoperative pain and nausea requirements comparing two minimally invasive surgical approaches.

Chen et al.,[14] in a recent publication, were the first authors to evaluate quality of life measures comparing different minimally invasive surgical approaches in general gynecology. They performed a prospective comparison between single-port laparoscopy and traditional multi-port laparoscopy to evaluate differences in patient outcomes. One hundred women were randomized to single-port versus traditional laparoscopy and multiple factors were compared. There were no differences in operative times, estimated blood loss, time to flatus, intraoperative or postoperative complications, or length of hospital stay. They did find, however, that postoperative pain was significantly less in the single-port patients based on lower total doses of postoperative narcotics administered and on lower visual pain scores. These findings were confirmed in a randomized study by Fagotti et al. [16] comparing conventional laparoscopy and laparoendoscopic single site surgery for adnexal disease.

In our study, we also evaluated visual pain scores at several different time points to determine whether there

TABLE 2 Median total postoperative intravenous analgesic and antiemetic doses

Analgesic and antiemetic	All laparoscopy, 2004–2010 ($n = 55$)	Laparoscopy, 2004–2006 ($n = 31$)	Laparoscopy, 2007–2010 ($n = 23$)	Robotic, 2007–2010 ($n = 30$)	p
Intravenous analgesics (mg)					
Total	26.7	28	26.2	10.7	0.003*
Range	0–293	0–155	0–293	0–86.7	
Dose/day	15.7	17	13.3	9.7	0.017**
Intravenous antiemetic (doses)					
Total	4	3	5.5	5	0.72
Total range	0–13	0–9	0–13	0–7	
Dose/day	2.4	1.3	3.3	3.0	0.40
Dose/day range	0–9	0–9	0–8	0–7	

* Robot is significantly different from laparoscopy 2004–2006 ($p = 0.0024$) and from laparoscopy 2007–2010 ($p = 0.0127$)

** Robot is significantly different from laparoscopy (2004–2006) ($p = 0.0153$)

TABLE 3 Reported median pain scores in the perioperative period

Pain score	Laparoscopy, 2004–2006 ($n = 22$)	Laparoscopy, 2007–2010 ($n = 17$)	Robot, 2007–2010 ($n = 29$)	p
Baseline				
Pain score	0	0	0	0.093
Range	0–4	0–9	0–1	
Preoperative				
Pain score	0	0	0	0.247
Range	0–4	0–3	0–3	
Postoperative				
Pain score	2.5	2	1	0.276
Range	0–10	0–8	0–10	
Discharge				
Pain score	2.5	0.5	1	0.641
Range	0–10	0–5	0–6	
Follow-up visit				
Pain score	0	0	0	0.624
Range	0–4	0–8	0–3	
Baseline to postoperative				
Change	2.5	2	1	0.556
Range	−3 to 10	−9 to 8	−1 to 10	
Baseline to discharge				
Change	2.5	0.5	1	0.589
Range	−4 to 4	−8 to 7	−1 to 3	

was a difference in perceived pain between the two surgical approaches. We found no difference in visual pain scores at baseline, preoperatively, postoperatively, or at the time of discharge. On the basis of these data, it is unclear whether the significant difference in total doses of IV opioids administered represents a true difference in benefit to the patients undergoing RRH when compared to LRH. Do we assume that a higher amount of medication was required to maintain a similar pain score? If so, what is the clinical relevance of taking additional pain medication if patients report the same level of comfort? Although it is difficult to interpret these results, further study in the differences in postoperative pain and nausea management, in addition to other measures of quality of life among MIS approaches in gynecologic oncology are warranted.

In 2009, the Gynecologic Oncology Group (GOG) published one of the only prospective randomized studies addressing quality of life in women undergoing exploratory laparotomy versus laparoscopic hysterectomy and staging for the treatment of early endometrial cancer.[17] As expected, the length of stay was shorter and the estimated blood loss was lower in the cases performed by laparoscopy, while the operative times were longer. The pathologic findings, surgical stage, and complication rates were similar among the two groups. In regard to quality of life measures, patients who underwent laparoscopy had higher Functional Assessment of Cancer Therapy-General (FACT-G) scores, better physical functioning, better body image, and earlier resumption of normal activities compared to the laparotomy group. Although the benefit in quality of life was primarily seen in the first 6 weeks after surgery, this study helped confirm what many physicians see in their patients undergoing minimally invasive surgery; a faster recovery time.

For this preliminary study comparing the robotic approach to traditional laparoscopy, we chose to look at a uniform group of patients, who underwent a complex procedure at a single institution, hoping to exclude factors that may contribute to any differences found between the two groups. Because of the retrospective nature, there are several limitations to the study. First, there was no reliable way to measure preoperative pain medication use. Second, because patients were not treated as part of a prospective protocol there were likely differences in physician practice that were difficult to quantify. The choice of opioid and antiemetic medication administered was at the discretion of the primary surgeon. Because of the small numbers per surgeon, we could not look specifically at physician practice pattern differences. Although this could account for some of the difference between the groups, it is routine practice to write both opioids and antiemetics as "prn" orders as opposed to scheduled doses. Therefore, the amount of

opioid and antiemetic medication administered should reflect the patient's needs. Finally, the visual pain scores were collected retrospectively, and therefore, it is unclear whether they were measured before or after pain medication was administered. In a prospective study, a pain medication algorithm could be developed so that narcotic administration would correlate with pain scores and therefore identify a true difference in narcotic use between two approaches. Although we recognize the limitations to the study, it is one of the first studies comparing postoperative pain and nausea between two MIS approaches in women with early cervical cancer.

In gynecologic oncology, the most important factor in deciding surgical approach is ultimately oncologic outcome and patient survival. If these can be maintained or even improved with the use of minimally invasive surgery, there is growing evidence supporting the advantages of minimally invasive surgery over traditional laparotomy.[13] We recently reported our data comparing all three surgical approaches to radical hysterectomy and pelvic lymph node dissection.[12] Like other authors, we found that both RRH and LRH resulted in shorter hospital stay, less blood loss, and fewer transfusions when compared to laparotomy. In addition, we found that in the RRH patients, the hospital stay was even shorter when compared to LRH although the clinical significance of this is unclear as it may reflect physician practice patterns. We are currently performing a cost comparison between RRH and LRH for the treatment of early cervical cancer, as this may also impact our current choice for surgical approach.

With the continued growth of minimally invasive surgery in gynecologic oncology, as well as the emergence of new minimally invasive surgical techniques, it is important for the practicing gynecologic oncologist to understand the implications of this technology on both oncologic outcomes as well as quality of life for our patients. Our preliminary data show that the robotic approach to radical hysterectomy and pelvic lymphadenectomy resulted in a significant decrease in intravenous opioid requirements compared to total laparoscopic radical hysterectomy; however, there was no difference in visual pain scores. In order to fully understand the differences in both medical outcomes, as well as quality of life, these surgical approaches will have to be compared in a prospective randomized fashion that use validated measures. In addition, we must ask ourselves whether the differences identified are clinically relevant to us or our patients.

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