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Intravenous Intraoperative Acetaminophen Reduces the Post-Operative Length of Stay in Patients Undergoing Robotic Assisted Surgery for Endometrial Cancer: IV Acetaminophen in Robotic Uterine Cancer Surgery

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Abstract

We sought to determine whether the use of intravenous acetaminophen (IV APAP) reduces the post-operative Length of Stay (LOS) in patients undergoing robotic assisted total laparoscopic hysterectomy with bilateral salpingo-oophorectomy with or without pelvic and para-aortic lymphadenectomy (RA-TLH/BSO w/wo PPLND) for the primary management of Endometrial Cancer (EMCA). We performed a retrospective cohort chart review of all patients who underwent a RA-TLH/BSO w/wo PPLND for EMC from January 1, 2010, to September 1, 2016, on a gynecologic oncology service in an integrated health care system. Of 256 patients identified in the cohort, 91 (36%) received IV APAP and 165 (64%) did not. After controlling for age, body mass index (BMI), year of procedure, operative time, hospital site, and operating surgeon, those patients who received IV APAP had a 42% reduction in post-operative LOS than patients who were not managed with IV AP intraoperatively (5.2 hours vs. 22.6 hours (p value < 0.001). Our data suggest that a multi-center prospective trial to validate our findings that the use of IV APAP achieves a significant reduction in the post-operative length of stay for patients undergoing robotic assisted surgery for endometrial cancer is warranted.

Keywords: Intra-Operative Intravenous Acetaminophen; Endometrial Cancer; Post-Operative Length of Stay; Robotic Assisted Hysterectomy

Introduction

The United States Federal Drug Administration approved the use of the Da Vinci™ robotic system for gynecologic surgery in 2005 [1]. Subsequently, robotic assisted laparoscopic hysterectomy with bilateral salpingo-oophorectomy with or without pelvic and para-aortic lymphadenectomy (RA-TLH/BSO w/wo PPLND) has become an increasingly common surgical approach for the treatment of endometrial cancer (EMCA). The benefits of the robotic assisted surgical approach include decreased intra-operative blood loss, decreased overall peri-operative morbidity, shortened post-operative recovery period, and a decreased hospital length of stay (LOS) when compared to laparotomy [2]. The primary objective of our study was to evaluate whether intraoperative IV Acetaminophen (IV APAP) is associated with a decreased LOS in women undergoing robotic hysterectomy for EMCA.

A secondary objective of our study was to determine whether IV APAP decreased the use of post-operative narcotic pain medications. With the growing epidemic of opioid addiction, there has been a national push to find alternative pain management regimens including the use of IV APAP and use of non-steroidal anti-inflammatory drugs. IV APAP administered in various forms including oral, rectal or intravenous (IV) and has been shown to

provide a synergistic analgesic effect when used in combination with traditional narcotic pain medications [3]. IV formulations have been shown to have a faster onset of action with more predictable pharmacokinetics with maximum plasma drug concentrations 2x that of oral and 4x that of rectal formulations at the same dosing [3]. The use of postoperative IV APAP has been studied in multiple surgical populations with variable conclusions [4-6]. In the obstetrical and gynecological literature, Altenau et al [7] performed a randomized double-blinded, placebo-controlled trial of IV APAP given for 48 hours postpartum in patients following cesarean section. They conclude that IV APAP was associated with a significant decrease in PO narcotic consumption but no difference in pain scores. Similarly, Herring et al [8] showed an overall decrease in opioid consumption of 26% in the total perioperative period with the addition of IV APAP to traditional opioid regimens in patients undergoing abdominal hysterectomy. While the use of postoperative IV APAP has been studied in multiple different surgical populations, the use of intraoperative IV APAP has been less well studied [9,10]. We hypothesized that the administration of intraoperative IV APAP would decrease LOS in patients undergoing RA-TLH/BSO for EMCA. Our secondary aims were to determine if administration of IV APAP had a significant impact on postoperative narcotic use, pain scores at the time of discharge, Estimated Blood Loss (EBL) or 30-day hospital readmission rates.

Materials and Methods

Following Institutional Review Board approval (#2016-0380) we performed a retrospective chart review of all patients who underwent RA-TLH/BSO at Geisinger Health System (GHS) between January 1, 2010 and September 1, 2016. Data was collected from two hospitals within our health care system. Variables including race/ethnicity, Body Mass Index (BMI), age at time of procedure, intraoperative and postoperative narcotic or non-narcotic pain medication, procedure time (skin incision to close), EBL, time from end of procedure to discharge (LOS), surgeon, 30-day readmission rate, and pain scores at discharge were abstracted from the medical record. The Numeric Rating Scale from 1-10 was used to assess pain. Patients whose procedures were converted to laparotomy or who did not have a final diagnosis of EMCA were excluded from the study. For the study group, 1 gram of IV APAP was administered during the intraoperative period, prior to transfer to the PACU.

Comparisons between the IV APAP and non-IV APAP groups were assessed using chi-Square test or Fisher's exact test for categorical variables and t-test or Wilcoxon rank sum test for continuous variables. Negative binomial regression models were used to predict LOS by controlling for other covariates. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). A p-value less than 0.05 was considered significant.

Results

We identified 256 patients who underwent RA-TLH/BSO for EMCA at GHS between January 1, 2010 and Sept 1, 2016. Of the study group, 91 (36%) patients received IV APAP (alone or in combination with narcotics) and 165 (64%) did not.

	No Intraoperative intravenous acetaminophen n=165	Received IV Intraoperative intravenous acetaminophen n=91	P-value
Body mass index, mean (STD)	35.65 (8.80)	38.84 (7.89)	0.0043
Age (years), (Standard deviation)	62.55 (10.96	62.48 (10.94)	0.9648
Pain score, median (Inter-quartile ratio)	2 (0, 4)	2 (0, 4)	0.2697
LOS (hours). median (Inter-quartile ratio)	22.60 (7.38, 25.95)	5.08 (4.20, 7.53)	<.0001
Length of procedure (hours), mean (Standard deviation)	2.81 (0.90)	2.46 (0.63)	0.0013
EBL (mL), median (Inter-quartile ratio)	50 (25, 100)	50 (25, 100)	0.5492
Readmission, n (%)	7 (4.24%)	2 (2.20%)	0.4979
Ketorolac, n (%)	81 (49.09%)	36 (39.56%)	0.1429
Post-operative narcotic use, n (%)	134 (81.21%)	77 (84.62%)	0.4935

Table 1. Descriptive analysis stratified by patients who did or did not receive IV APAP.Table 1 describes the variables compared between the two patient groups. The group who received IV APAP had a higher average BMI (38.8 vs. 35.6) and shorter procedure time (2.8 vs 2.5 hours) than the control group. No difference was noted in average pain score at time of discharge (2) or age at time of procedure (62 years) between the 2 groups. Most patients included in the study were Caucasian, which is consistent with the patient population of the geographic area. There was no significant difference in EBL between the two groups. The data showed the median blood loss of 50 mL with a interquartile range of 25-100mL

for both groups of patients. Thirty-day readmission rate for the IV APAP group was 2.20% (2 patients) compared to 4.24% (7 patients) in the control group (p-value 0.49). Only one patient, in the control group, was admitted secondary to abdominal pain and shortness of breath. The remainder of the patients were admitted for infectious complications. The median LOS of patients who received IV APAP was 5.08 hours (IQR: 4.20-7.53) as compared to 22.60 hours (IQR: 7.38-25.95) for those patients who did not receive IV APAP, (p-value <0.0001). The percentage of patients who received ketorolac was also compared between the two groups and showed no significant difference (39.5% vs. 46.7%; p-value= 0.2731).

We next evaluated whether intraoperative IV APAP decreased postoperative narcotic use. Of the 91 pts who received IV APAP, 77 (84.6%) received postoperative narcotics, compared to 134 of the 165 (81.2%) patients who did not receive IV APAP. Our data showed that IV APAP had no significant impact on the percentage of patients requiring postoperative narcotics (p = 0.49). We further evaluated LOS based on postoperative narcotic use. Patients who received IV APAP and no postoperative narcotic (n=14) had the lowest LOS at 4.24 hours and patients who had no IV APAP and received postoperative narcotic (n=134) had the highest LOS at 23.09 hours. The median LOS for patients receiving postoperative narcotics was 19.68 hours (IQR: 5.08-25.00) and 6.67 hours (IQR: 4.20-22.60) for patients not using postoperative narcotics (p-value 0.0080). To identify if the use of ketorolac rather than APAP was a significant factor in LOS, data was examined for various analgesia combinations. The median LOS (IQR 13.13, 23.50) for the 12 patients who received ketorolac only was 22.59 hours, which was similar to the LOS for patients who did not receive IV APAP. The combination of IV APAP and ketorolac without narcotics showed the shortest LOS at 3.90 hours suggesting that IV APAP rather than ketorolac contributed to the decrease in LOS.

To evaluate whether age, year of surgical procedure, BMI, length of procedure, hospital site or surgeon were confounding variables in LOS, univariate and multivariate analysis were performed (Table 2). In an unadjusted model, the LOS for patients using IV APAP is 0.43 (CI: 0.35, 0.54) times the LOS for patients who did not receive IV APAP. After adjusting for age, attending, BMI, length of procedure, hospital site and year, the LOS for patients using IV APAP is 0.58 (CI: 0.44, 0.77) times of LOS for patients who did not receive IV APAP. Our data suggest that intraoperative IV APAP was an independent predictor of decreased LOS in our study population.

	No Intraoperative intravenous acetaminophen	Received IV Intraoperative intravenous acetaminophen	Ratio (95% CI)	P- value
Unadjusted results				
LOS (hours), Mean (95% CI)	23.52, (20.66, 26.78)	10.15 (8.46, 12.16)	0.43 (0.35, 0.54)	<.0001
Adjusted Results				
LOS (hours), Mean (95% CI)	10.45 (4.02, 27.16)	6.1 (2.25, 16.56)	0.58 (0.44, 0.77)	<.0001

Table 2: Multivariate analysis of relationship between IV APAP use and LOS.

Discussion

To our knowledge, we are the first study to evaluate the effects of intraoperative IV APAP on LOS in a robotic surgery gynecologic population. Our data suggests a role for IV APAP in decreasing post-operative LOS in patients undergoing RA-TLH/BSO for a gynecologic malignancy. The advantages of our study included the ability to identify and control for associated factors affecting LOS and to assess for multiple outcomes through a well categorized Electronic Medical Record (EMR). All robotic cases are booked as outpatient surgeries and counselled in a similar fashion by the same team. Of note, an Enhanced Recovery after Surgery program had not been implemented at our institution during the time of this study. To account for the possibility that the difference in LOS was related to surgeon, year of procedure, location, age of the patient or procedure time, a negative binomial regression analysis was performed. Our multimodal analysis model showed that IV APAP was a significant factor in decreasing LOS when the model was adjusted by age, year, individual surgeon, BMI, location and procedure time. Although lymphadenectomy was not a variable that we abstracted, the similar procedure time suggests that it did not uniquely contribute to the LOS.

Unlike the results of previous studies, our study did not show that the use of IV APAP decreased post-operative pain or decreased the usage of post-operative narcotic pain medications. It is, however, possible that the while pain scores were similar in both groups, the patients who received IV APAP may have may have experience a shorter period of post-operative sedation, therefore allowing earlier ambulation and earlier accomplishment of post-operative discharge criteria milestones. One possible explanation for our finding

of similar pain scores in both groups, was that narcotic use was identified as a "yes or no" variable and not quantified. We would propose that post-operative narcotic use should be quantified in future prospective studies.

Our study is limited by the fact that was a retrospective chart review with a small sample size and a homogenous Caucasian population. Given the retrospective nature of the study, confounding factors such as timing of intraoperative APAP administration, ancillary staff, IV fluid administration, patient comorbidities, hospital discharge processes, institutional variables and socioeconomic factors may additionally be responsible for this decrease. Data was collected from 2 separate institutions which made it difficult to eliminate institutional factors that may have played an important role in LOS.

A cursory review of cost at our institution identified the J code cost of one 10mg/mL (1000_{mg}) vial of IV APAP at $30.93 while 650 mg oral forms cost $0.06 and 650 mg rectal suppository cost $0.17. Thus, while our data utilized only IV APAP, alternate routes of administration or preoperative administration may provide the same effect at a lower cost. With PACU costs in the studied health system approximating $35/per minute, an overall decreased LOS has the potential to significantly decrease health care costs for these patients.

Our data, therefore, suggest that a multi-center prospective trial to validate our findings showing that the use of IV APAP achieves a significant reduction in the post-operative length of stay for patients undergoing robotic assisted surgery for EMCA is warranted.

Conclusion

In our retrospective review of 256 patients undergoing robotic assisted surgery for the primary management of EMCA, we found that the use of intra-operative IV APAP significantly reduced the post-operative hospital LOS by 42%. On the other hand, we did not find a difference in post-operative pain scores for patients receiving intra-operative IV APAP compared with those who did not. Given the importance of hospital length of stay initiatives, our data suggest that a multi-center prospective trial to validate our findings is warranted.

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