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IMPLEMENTATION SCIENCE & OPERATIONS MANAGEMENT

Impact of Gabapentin on PACU Length of Stay and Perioperative Intravenous Opioid Use for ERAS Hysterectomy Patients

Dan B. Ellis[1] · Rachel Sisodia[2] · Meryl Paul[3] · Kai Qiu[1] · Michael K. Hidrue[4] · Sheri Berg[1] · Jevon Oliver[5] · Marcela G. del Carmen[4]

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Abstract

We investigated the impact of preoperative gabapentin on perioperative intravenous opioid requirements and post anesthesia care unit length of stay (PACU LOS) for patients undergoing laparoscopic and vaginal hysterectomies within an Enhanced Recovery After Surgery (ERAS) pathway. A multidisciplinary team retrospectively examined 2,015 patients who underwent laparoscopic or vaginal hysterectomies between October 2016 and January 2020 at a single academic institution. The average PACU LOS was 168 min among patients who did not receive gabapentin vs. 180 min both among patients who received ≤ 300 mg of gabapentin and patients who received > 300 mg of gabapentin. After adjusting for demographics and medical comorbidities, PACU LOS for patients given ≤ 300 mg gabapentin was 6% longer (rate ratio (RR) = 1.06, 95% CI = 1.01–1.11) than for patients who were not given gabapentin, and for patients who received > 300 mg of gabapentin was 7% longer (RR = 1.07, 95%CI = 1.01–1.13) than for those who did not receive gabapentin. Patients who received ≤ 300 mg gabapentin received 9% less perioperative intravenous hydromorphone than patients who did not receive gabapentin (RR = 0.91, 95% CI = 0.86 – 0.97); patients who received > 300 mg of gabapentin received 12% less perioperative intravenous hydromorphone than patients who did not receive gabapentin (RR = 0.88, 95% CI = 0.82 – 0.95). These findings represent an absolute difference of 0.09 mg intravenous hydromorphone. There were no statistically significant differences in total intravenous fentanyl received. Preoperative gabapentin given as part of an ERAS pathway is associated with statistically but not clinically significant increases in PACU LOS and decreases in total perioperative intravenous opioid use.

Keywords PACU · Gabapentin · Opioids · ERAS · Efficiency

This article is part of the Topical Collection on *Implementation Science & Operations Management*

✉ Dan B. Ellis
dbellis@mgh.harvard.edu

Rachel Sisodia
rsisodia@mgh.harvard.edu

Meryl Paul
mpaul15@partners.org

Kai Qiu
kqiu@partners.org

Michael K. Hidrue
mhidrue@partners.org

Sheri Berg
Sheriberg@gmail.com

Jevon Oliver
Joliver0@mgh.harvard.edu

Marcela G. del Carmen
mdelcarmen@mgh.harvard.edu

[1] Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

[2] Department of Gynecology Oncology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

[3] Department of Anesthesiology, Salem Hospital, 81 Highland Avenue, Salem, MA 01970, USA

[4] Massachusetts General Physicians Organization, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

[5] Director, Pharmacy Services, Integrated Care, Mass General Brigham, 399 Revolution Drive, Suite 950, Somerville, MA 02145, USA

Introduction

As Enhanced Recovery After Surgery (ERAS) pathways expand across institutions and into more surgical subspecialties, clinicians are continually working to more efficiently move patients through perioperative environments. Historically, opioids have been the primary modality to treat postoperative pain. However, escalating opioid doses prolong time spent in the post anesthesia care unit (PACU), decrease bowel function, and increase the incidence of nausea and vomiting. These untoward effects, when combined with the opioid epidemic and financial pressures placed upon healthcare systems to increase patient throughput, provide the impetus to minimize opioid administration and turn to non-opioid analgesics [1, 2].

Twenty years ago, clinicians began introducing gabapentin to surgical pathways as they explored novel uses for non-traditional analgesics [3, 4]. Since perioperative pain treatment traditionally focused on opioids and anti-inflammatory agents, gabapentin offered an alternate pathway not traditionally tied to nociception [5–7]. The results of this intervention can be seen in Dierking's randomized, double-blind trial in 2004, which showed that larger doses of gabapentin could reduce postoperative morphine consumption following abdominal hysterectomy [8]. This finding was further substantiated by Doleman et al. metanalysis of 133 studies, which demonstrated that preoperative gabapentin decreased cumulative 24-h morphine-equivalent consumption and pain scores at 1, 2, 6, 12, and 24 h [9]. Additional studies supported the opioid-sparing effects of gabapentin [9–11]. In contrast, a recent meta-analysis by Verret et al. did not find a clinically significant analgesic effect from perioperative use of gabapentinoids [12].

As pre-operative gabapentin administration became more common at our institution, anecdotal reports by perioperative staff of increased postoperative somnolence with gabapentin surfaced. Our staff specifically observed this trend in patients enrolled in ERAS hysterectomy: patients who received large quantities of pre-operative gabapentin tended to have increased postoperative somnolence and prolonged PACU stays. Postoperative somnolence is not necessarily undesirable. However, delayed PACU discharge can inhibit efficient flow through perioperative arenas and postoperative somnolence may potentially delay ambulation [13].

While a decrement in consciousness, which can be intuited from gabapentin's action on the gamma aminobutyric acid (GABA) pathway, is substantiated by current relevant literature, pre-operative gabapentin has been correlated with but not definitively linked to time spent in the PACU in ERAS patients [5, 9, 15]. A retrospective analysis in 2018 by Siddiqui et al. demonstrated an increase in PACU LOS in 228 ERAS patients who received gabapentin. This study was not specific to ERAS hysterectomy patients, and it incorporated a variety of anesthetic techniques [15]. A randomized controlled trial by Li et al. in 2019 examined patients who received hysterectomy with colporrhaphy. This study did not find a difference in opioid consumption, pain, or recovery room stays in patients who received gabapentin when compared to placebo. However, limitations of this study include a small sample size and a lack of control for anesthetic type [16].

To specifically address the above questions and further refine our current and future ERAS pathways, we formed a multidisciplinary team to examine the impact of gabapentin on PACU LOS and perioperative opioid use for ERAS laparoscopic and vaginal hysterectomy patients. The study was intended to influence the presence and dosage of gabapentin in our current and future ERAS pathways.

Materials and methods

Approval was obtained through the Institutional Review Board (IRB) at the Massachusetts General Hospital (IRB: 2017P000443). At our institution, all laparoscopic and vaginal hysterectomy patients are automatically enrolled in the ERAS pathway. Requirement for written informed consent was waived by the IRB. This study focused exclusively on patients who were scheduled for day surgery. A total of 2,219 consecutive charts between October of 2016 and January of 2020 were retrospectively reviewed.

The primary outcome variable for our study was minutes spent in the PACU, or PACU LOS. This was defined as the difference in time between arrival in PACU and the time when a patient met criteria for discharge from the PACU, as determined by the modified Aldrete score. This validated and widely-accepted score is a composite index of pain control, level of consciousness, nausea, vital signs, ambulation, ability to tolerate food/liquid, and urine output [14]. We also examined the impact of preoperative gabapentin on the amount of perioperative intravenous opioids required, defined as the total doses of intravenous fentanyl and hydromorphone given to each patient on the day of surgery.

The exposure variable in our study was the quantity of preoperative gabapentin administered. Most patients who were given preoperative gabapentin received either 300 mg or 600 mg. However, a few patients received less than 300 mg of gabapentin, between 300 and 600 mg of gabapentin, and more than 600 mg of gabapentin. To facilitate comparisons, we grouped patients into three categories of gabapentin dose: none, 300 mg or less, and more than 300 mg.

To control for confounding factors, we adjusted for patient age, body mass index, American Society of

Anesthesiologist (ASA) category, presence of diabetes, and quantity of intra-operative anesthesia medications that correlate with altered consciousness in the postoperative period (midazolam, fentanyl, hydromorphone, and haloperidol). We also stratified our patients by year of surgery, to account for changes in overall PACU LOS and opioid use patterns across our institution during the time covered by this study.

Of note, patients were cohorted into three groups: patients less than 45 years of age; patients between 45 and 65 years of age; and patients > 65 years of age based on feedback from PACU nursing staff. During the design of this study, our hospital's nursing staff commented that younger patients who received gabapentin tended to recover faster than older patients. To examine this claim more thoroughly, patients were divided into these three age groups.

Demographic and medical characteristics were summarized using descriptive statistics. We used T-test and one-way Analysis of Variance (ANOVA) to assess the difference in average PACU LOS between categories of a covariate. We then used a generalized linear model to assess the independent association of covariates on PACU LOS. All statistical tests were two-sided and P-values of < 0.05 were used to indicate statistical significance. Regression results are reported as rate ratios. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

We excluded patients who deviated substantially from our ERAS pathway as our primary aim is to review the impact of preoperative gabapentin on PACU LOS within the context of ERAS. As midazolam is not part of the pathway, patients who received more than 2 mg were excluded from our analysis. At our institution, the vast majority of patients received either no midazolam or 2 mg of midazolam, and exceptionally few patients received 1 mg of midazolam. Therefore, to minimize confusion, patients who received 1 mg of midazolam were also excluded from analysis.

Additionally, patients who received more than 2 mg of haloperidol or 2.5 mg of intravenous hydromorphone were excluded, as such high doses similarly were clear deviations from our ERAS protocols. We also excluded patients who were documented as receiving more than 500mcg of fentanyl, as these records either reflect substantial pre-existing opioid tolerance or data error, for example with misclassification of remifentanil infusions. Finally, we excluded patients with extremely prolonged PACU LOS of over 500 min as these outliers, who represent less than 1% of charts reviewed, most likely reflected perioperative complications unrelated to our interventions of interest.

Results

After reviewing 2,219 charts and excluding outliers using the above criteria, our final data set contained 2,015 patients who underwent laparoscopic or vaginal hysterectomy between October 2016 and January 2020. The breakdown of patients by demographic variables and medication doses is given in Table 1. A total of 204 patients were excluded; please see Table 2 for a breakdown of exclusions by rationale.

The average PACU length of stay for all patients after vaginal or laparoscopic hysterectomies was 172 min. The distribution of PACU LOS is seen in Fig. 1. We found a statistically significant difference in PACU LOS between patients who were given gabapentin and those who were not. The average PACU LOS was 168 min in patients who did not receive gabapentin vs. 180 min in both patients who were given less than or equal to 300 mg of preoperative gabapentin, and in patients who were given more than 300 mg of gabapentin. Figure 2 shows the distributions of PACU LOS for each of these subsets.

Table 3 displays the results of the multivariable regression to identify factors that influence PACU LOS. After adjusting for potential confounders such as age, BMI, ASA category, diabetes, type of surgery (laparoscopic vs vaginal), and year of surgery, the analysis found that administration of 300 mg or less of gabapentin was associated with a 6% increase (rate ratio (RR) = 1.06, 95% CI = 1.01–1.11) in PACU LOS when compared to no gabapentin. Administration of more than 300 mg of preoperative gabapentin was associated with a 7% increase (RR = 1.07, 95%CI = 1.01–1.13) in PACU LOS vs. no gabapentin. There was no difference in PACU LOS between patients who received 300 mg or less gabapentin vs. those who received more than 300 mg.

We also examined the association between gabapentin and total intravenous perioperative (day-of-surgery) opioid dose. After adjustment for confounders as above, patients who were given 300 mg or less of pre-operative gabapentin received 9% less perioperative intravenous hydromorphone (95% CI = 3%–14%) compared to patients who did not receive gabapentin. Similarly, we found that patients who were given more than 300 mg of gabapentin received 12% less perioperative intravenous hydromorphone (95% CI = 5%–18%). There were no statistically significant differences in perioperative intravenous fentanyl dose across the three patient groups. Please see Table 4 for more details.

Discussion

Our study addresses the impact of pre-operative gabapentin administration on PACU LOS for ERAS hysterectomy patients. Within the context of ERAS, in which patients may

Table 1 Sample Distribution and PACU Time by Demographic and Clinical Factors

Covariates	Sample Distribution, N (%)	PACU (minutes), Mean (STD)	Fentanyl(mcg), Mean (STD)	Hydromorphone (mg), Mean (STD)
Age Group				
< = 45 Yrs	587 (29.1)	167 (72)	164 (88)	0.89 (0.62)
46–64 Yrs	924 (45.9)	173 (74)	151 (89)	0.78 (0.57)
> = 65 Yrs	504 (25.0)	177 (84)	144 (82)	0.66 (0.51)
BMI Category				
Normal	622 (30.9)	170 (76)	145 (81)	0.70 (0.54)
Overweight	573 (28.4)	172 (76)	153 (93)	0.78 (0.59)
Medium Obese	397 (19.7)	172 (78)	157 (90)	0.87 (0.58)
Sever Obese	423 (21.0)	173 (75)	160 (85)	0.81 (0.58)
ASA Category				
Healthy	160 (7.9)	166 (73)	151 (82)	0.69 (0.58)
Mild	1293 (64.2)	171 (75)	158 (88)	0.81 (0.57)
Severe	348 (17.3)	172 (76)	146 (82)	0.75 (0.58)
Missing	214 (10.6)	182 (81)	135 (90)	0.72 (0.56)
Diabetic				
Yes	185 (9.2)	180 (74)	153 (92)	0.75 ().57)
No	1830 (90.8)	171 (76)	153 (87)	0.78 (0.58)
Surgery Type				
Laparoscopic	1831 (90.9)	170 (74)	154 (87)	0.79 (0.58)
Vaginal	184 (9.1)	193 (92)	144 (88)	0.61 (0.46)
Midazolam				
0 mg	660 (32.8)	177 (80)	138 (89)	0.60 (0.53)
2 mg	1355 (67.2)	170 (74)	160 (85)	0.86 (0.58)
Haloperidol				
0 mg	649 (32.2)	169 (78)	157 (88)	0.77 (0.58)
1 mg	1366 (67.8)	173 (75)	151 (87)	0.78 (0.58)
Gabapentin				
0 mg	1329 (66.0)	168 (74)	156 (88)	0.84 (0.59)
< = 300 mg	410 (20.4)	180 (80)	148 (85)	0.67 (0.49)
> 300 mg	276 (13.7)	180 (78)	145 (88)	0.64 (0.56)
Surgery Year				
2016	157 (7.8)	149 (68)	211 (87)	1.12 (0.54)
2017	610 (30.3)	166 (72)	167 (82)	0.98 (0.58)
2018	571 (28.3)	181 (79)	129 (93)	0.55 (0.58)
2019	584 (29.0)	173 (77)	151 (80)	0.70 (0.48)
2020	93 (4.6)	187 (76)	128 (65)	0.77 (0.47)

be discharged as early as the day of surgery, time spent in the PACU can have outsized effect on patient throughput. We found that preoperative gabapentin was associated with a statistically significant increase in PACU LOS.

Notably, while the impact of gabapentin on PACU LOS reached statistical significance, the effect size was small. The increase of approximately 7% or 12 min in PACU LOS as identified in our study is unlikely to have a noticeable impact on hospital efficiency or patient throughput, especially considering that the total time between patient check-in and PACU discharge for these patients often extends to beyond 8 h. Though prolonged PACU delays can have wide-ranging consequences on the operating efficiency of hospitals and

Table 2 Patients Excluded from Analysis

Covariates	Sample Distribution, N (%)
Midazolam	
More than 2mgs given	34 (1.5%)
Haloperidol	
More than 2 mg given	11 (0.5%)
Fentanyl	
More than 500 mcg given	93 (4.2%)
Hydromorphone	
More than 2.5 mg given	45 (2.0%)
PACU Time	
More than 500 min	21 (0.9%)

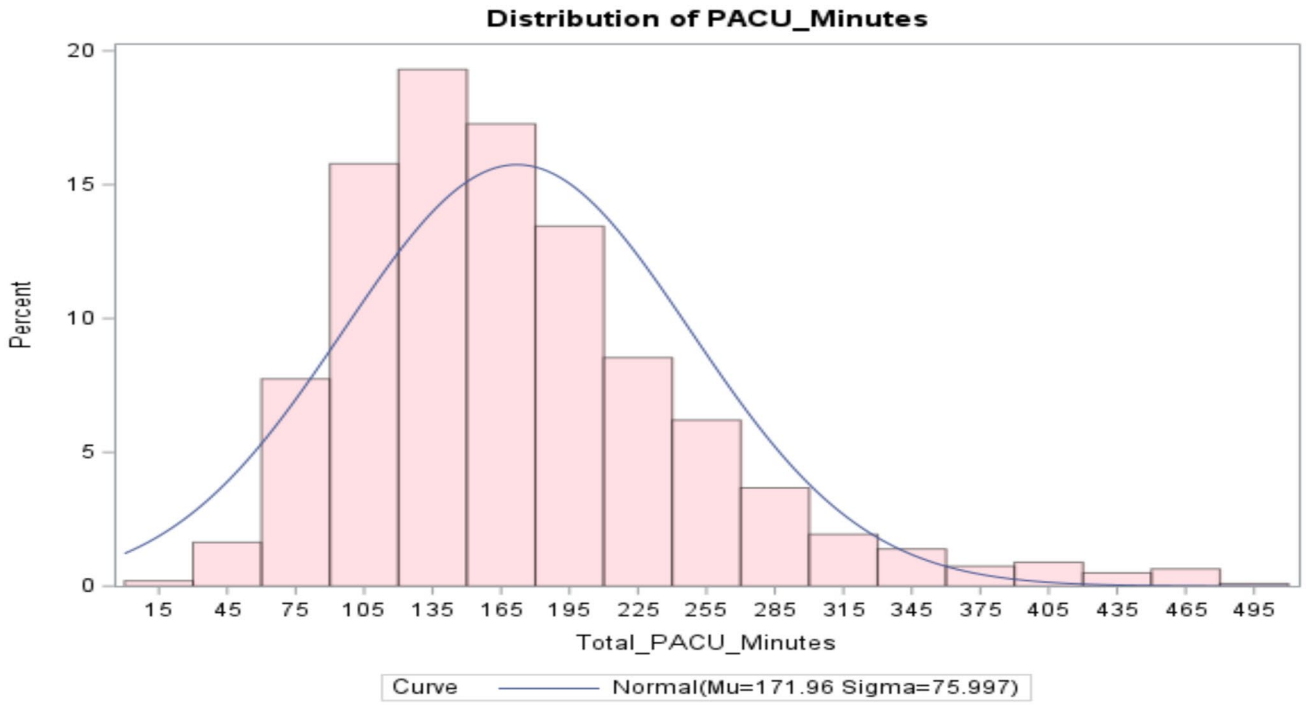

Fig. 1 Distribution of PACU LOS for all study patients

surgical centers [13], interventions that affect PACU LOS to the extent that preoperative gabapentin did in this study are unlikely to be clinically significant.

Our study also demonstrated a statistically significant decrease in perioperative intravenous hydromorphone use when patients receive preoperative gabapentin. This

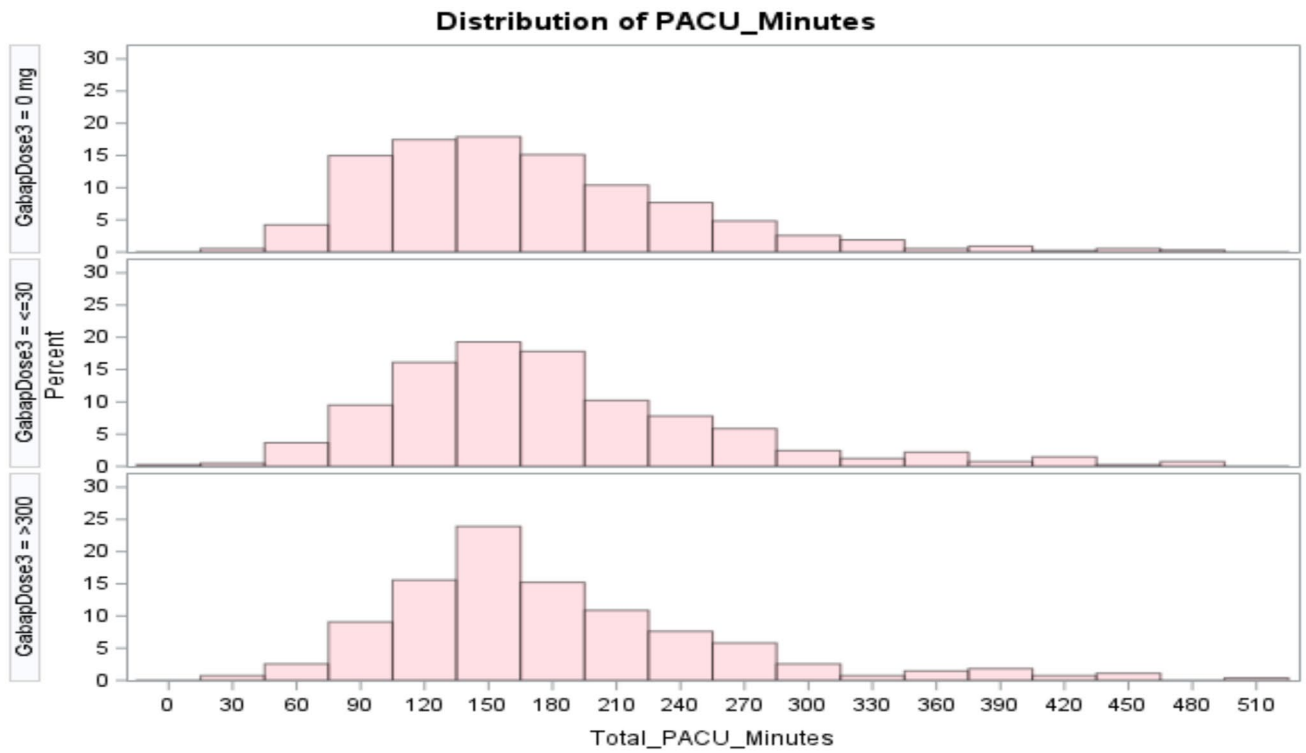

Fig. 2 Distribution of PACU LOS by Gabapentin Dose

Table 3 Regression Results Demonstrating Associations with PACU LOS*

Covariates	PACU LOS Rate Ratio	
	Estimate	[95% CI]
Age (ref > = 65 Years)		
46–64 Years	0.99	[0.94 – 1.04]
< = 45 Years	0.95	[0.90 – 1.01]
Diabetic (ref = non-diabetic)	1.04	[0.97 – 1.11]
Vaginal (ref = Laparoscopic)	1.14	[1.07 – 1.21]
ASA (ref = Mild, or II)		
Healthy, or I	1.00	[0.93 – 1.07]
Severe, or III-IV	0.98	[0.93 – 1.03]
BMI (ref = Normal)		
Overweight	1.00	[0.96 – 1.05]
Obese	0.99	[0.94 – 1.05]
Severely Obese	1.02	[0.96 – 1.08]
Midazolam (ref = 0)	0.99	[0.95 – 1.04]
Haloperidol (ref = 0)	1.04	[1.00 – 1.08]
Fentanyl in mg	0.96	[0.77—1.20]
Hydromorphone in mg	1.07	[1.03 – 1.10]
Year (ref = 2016)		
2017	1.12	[1.04 – 1.21]
2018	1.23	[1.13 – 1.33]
2019	1.16	[1.07 – 1.26]
2020	1.26	[1.12 – 1.40]
Gabapentin (ref = 0)		
< = 300	1.06	[1.01 – 1.11]
> 300	1.07	[1.01 – 1.13]

*The estimates are in rate ratio scale. For example, the estimate for vaginal surgery is 1.14 [95% CI = 107–1.21]. It implies those who had vaginal surgery, holding everything else equal, on average stayed 14% longer than those who had a laparoscopic surgery. A parallel interpretation can be constructed for the other covariates

Table 4 Regression Demonstrating Associations with Cumulative Perioperative Intravenous Opioid Dose*

Parameter	Hydromorphone		Fentanyl	
	Rate Ratio	[95% CI]	Rate Ratio	[95% CI]
Age (ref > = 65 Years)				
46–64 Years	1.12	[1.06 – 1.20]	1.05	[1.00 – 1.11]
< = 45 Years	1.24	[1.15 – 1.33]	1.12	[1.05 – 1.19]
Vaginal (ref = Laparoscopic)	0.89	[0.82 – 0.97]	0.98	[0.91 – 1.05]
Diabetic (ref = non-diabetic)	0.99	[0.91 – 1.07]	1.03	[0.95 – 1.11]
ASA (ref = Mild or II)				
Healthy or I	0.92	[0.84 – 1.01]	0.95	[0.88 – 1.03]
Severe or III-VI	1.03	[0.96 – 1.10]	0.95	[0.90 – 1.01]
BMI (ref = Normal)				
Overweight	1.12	[1.05 – 1.19]	1.07	[1.02 – 1.13]
Obese	1.16	[1.08 – 1.24]	1.08	[1.02 – 1.15]
Severely Obese	1.11	[1.03 – 1.19]	1.09	[1.03 – 1.16]
Surgery Year(ref = 2016)				
2017	0.93	[0.85 – 1.01]	0.80	[0.74 – 0.86]
2018	0.79	[0.72 – 0.87]	0.71	[0.65 – 0.77]
2019	0.72	[0.65 – 0.78]	0.71	[0.66 – 0.78]
2020	0.75	[0.65 – 0.85]	0.62	[0.55 – 0.70]
Midazolam (ref = 0)	1.06	[1.00 – 1.12]	1.01	[0.96 – 1.06]
Haloperidol (ref = 0)	0.97	[0.92 – 1.02]	0.97	[0.93 – 1.01]
Gabapentin (0 mg)				
< = 300 mg	0.91	[0.86 – 0.97]	1.00	[0.95 – 1.05]
> 300 mg	0.88	[0.82 – 0.95]	0.97	[0.91 – 1.03]

*These estimates are in rate ratio scale. For example, in the Hydromorphone model, the estimate for vaginal surgery is 0.89 [95% CI = 0.82–0.97]. It implies those who had vaginal surgery, holding everything else the same, on average used 11% less hydromorphone than those who had a laparoscopic surgery and this difference is statistically significant

correlates with other findings in the literature. However, it is unclear whether this reduction is due to lower pain levels or to increased patient somnolence, thereby decreasing the frequency of requests for pain medications. In addition, the absolute difference in cumulative opioid dose were small. Among patients who did not receive gabapentin, the average total perioperative intravenous hydromorphone dose was 0.86 mg. As such, our study found that preoperative gabapentin use was associated with a decrease of approximately 0.09 mg intravenous hydromorphone, equivalent to only a fraction of typical single doses given in the PACU. This reduction in perioperative intravenous opioid use associated with gabapentin usage is also therefore of little to no clinical significance.

Taken together, the results of our study of ERAS hysterectomy patients indicate that preoperative gabapentin prolongs PACU LOS and reduces postoperative opioid requirements, but that both effects are clinically insignificant in magnitude. As our field continues to expand and improve ERAS initiatives, our study suggests that gabapentin may play only a very limited role in promoting postoperative recovery.

Our study has several limitations. Its retrospective nature weakens our ability to establish causality. During the study period, our institution continued to simultaneously create and implement additional ERAS pathways, potentially confounding our data. Our results may also have limited generalizability, as our study specifically focused on ERAS hysterectomy patients. Further, while we excluded PACU stays of longer than 500 min (0.94% of total population) from our analysis, our study does not address urinary retention or intractable post-operative nausea as potential causes of delayed discharge from the PACU, which may also confound our data. This remains an area of ongoing research at our institution.

Finally, there is a potential for temporal variation in gabapentin administration and the time course of the study period. While ERAS Hysterectomy patients received a wide variety of gabapentin doses throughout the examined time period, it is possible that the activation of additional ERAS pathways such as mastectomy with immediate reconstruction could have impacted gabapentin administration patterns over time.

Conclusions

In our study of hysterectomy patients enrolled in ERAS pathways, preoperative gabapentin administration was associated with two statistically significant effects: increase in PACU LOS and decrease in perioperative opioid requirements. However, both the PACU LOS and opioid requirement effect sizes were small and unlikely to be clinically significant.

Authors' contributions All authors contributed text to the manuscript. Dan Ellis, Rachel Sisodia, and Marcela del Carmen helped design and implement the ERAS pathway.

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Availability of data and material The retrospective data collected and analyzed for this study are available for examination if requested.

Code availability SAS code used for statistical analysis is available for examination if requested.

Declarations

Ethics approval IRB 2017P000443 at Massachusetts General Hospital.

Consent to participate Waived by IRB.

Conflicts of interest/competing interests The authors declare no conflicts of interest.

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