Contents lists available at ScienceDirect

Asia-Pacific Journal of Oncology Nursing

Original Article

Implementation of an enhanced recovery protocol in patients undergoing mastectomies for breast cancer: an interrupted time-series design

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ABSTRACT

Background: We reviewed internal data and the current literature to update our enhanced recovery protocol (ERP) for patients undergoing a total breast mastectomy. Following implementation, the protocol was audited by chart review and compliance reminders were sent through email.
Objective: Our primary research aim was to examine the protocol compliance following the update. Our secondary aims were to examine the association between the change in protocol and the rates of postoperative nausea and vomiting (PONV) and hematoma formation requiring reoperation.
Methods: We retrospectively obtained data extracted from the electronic medical record. To test for a difference in outcomes before versus after implementation of the protocol we used multivariable logistic regression with the primary comparisons excluding a $\pm$ one-month window and secondary comparisons excluding a $\pm$ three-month window from the date of implementation.
Results: Our cohort included 5853 unique patients. Total intravenous anesthesia (TIVA) compliance increased by 17%–52% ($P < 0.001$) and the use of intraoperative ketorolac dropped from 44% to nearly no utilization (0.7%; $P < 0.001$). The rate of reoperation due to bleeding decreased from 3.6% to 2.6% after implementation with the adjusted decrease being 1.0% (bootstrap 95% CI, 0.11%, 1.9%; $P = 0.053$) excluding a $\pm$ 1 month window and 1.2% (bootstrap 95% CI, 0.24%, 2.0%; $P = 0.028$) excluding a $\pm$ 3-month window. The rate of rescue antiemetics dropped by 6.4% (95% CI, 3.9%, 9.0%).
Conclusions: We were able to improve compliance for nearly all components of the protocol which translated to a meaningful change in an important patient outcome.

Introduction

In 2016, our institution, Memorial Sloan Kettering Cancer Center, opened a free-standing ambulatory surgery center, the Josie Robertson Surgery Center, to perform complex cancer surgeries in an outpatient setting.[1] We implemented an enhanced recovery protocols (ERP) to standardize and optimize care.[2] One of the primary endpoints of the total breast mastectomy ERP was the reduction of postoperative nausea and vomiting (PONV), which can lead to dehydration, wound dehiscence, pain, immobility, increased length of hospital stays, and decreased patient satisfaction.[3] We initially presented the protocol at a departmental meeting, and then distributed printed copies to each of the operating

rooms for reference. Between January 4, 2016 and December 31, 2018, our rates of postoperative nausea and vomiting rescue administration dropped by 28% in patients undergoing mastectomies (95% CI, 22–36).[2]

As a part of continuous improvement, we reassessed our guidelines based upon our internal data and updated literature. The review of our outcomes led to a creation of a new protocol to address the disproportionate incidence of extended stays due to PONV in patients undergoing outpatient plastic reconstruction following total breast mastectomy.[4] The implementation of a new ERP protocol in this population led to the increased use of total intravenous anesthesia (TIVA) and a significant decrease in rates of PONV rescue medication and extended stay due to PONV.[4] Following the successful implementation of the protocol in the

outpatient plastic reconstruction surgeries, a collaborative task force created a similar protocol for patients undergoing total breast mastectomy with or without reconstruction based on the most up to date literature and our internal data.[5]

The total breast mastectomy ERP updates targeted the patient outcomes of PONV and reoperation due to hematoma formation. To address PONV, the protocol focused on identifying predictors of PONV and the implementation of interventions to reduce the risk in high-risk populations including the addition of TIVA.[3,6–9] In addition, following an analysis of our internal data between January 2016 and June 2019, we concluded that ketorolac increased the risk of reoperation due to bleeding (odds ratio 2.43; 95% CI, 1.60–3.70; $P < 0.0001$) and removed the administration of ketorolac from the protocol.[10]

The protocol was presented to all anesthesia providers through a single staff meeting and email on May 1, 2020. Following implementation, the protocol was audited by Certified Registered Nurse Anesthetists performing chart reviews and compliance reminders were sent through email if the protocol was not followed. Our primary research aim was to examine the protocol compliance following the protocol implementation. Our secondary aim was to examine the association between the change in protocol and the rates of postoperative nausea and vomiting and hematoma formation requiring reoperation to examine whether our updated protocol improved patient outcomes.

Methods

After institutional review board approval, we retrospectively obtained data extracted from the electronic medical record (EMR). In order to identify which reoperations were a result of a hematoma, we identified all reoperations within 30 days following the initial breast surgery, then manually completed a chart review to exclude unrelated procedures or incision and drainage surgeries required due to. Although more patients may have developed a hematoma that did not require a surgery to address, we defined our endpoint to be those who required additional surgery to evacuate the hematoma.

First, we assessed whether we needed to account for temporal trends. To do so we investigated the association between the outcomes and date of surgery among those treated before implementation using separate multivariable logistic regression models; the model predicting reoperation due to hematoma formation was adjusted for age, body mass index (BMI), bilateral surgery, reconstruction procedure, use of antiplatelet and use of an anticoagulant and the model predicting requiring PONV rescue was adjusted for age and Apfel score (0–2, 3, vs 4). In scenarios where we did not find evidence of a temporal trend we used multivariable logistic regression to test the association between study period and the outcomes and used this model to calculate an adjusted difference in the risk of the outcomes by study period along with confidence intervals around the adjusted differences generated using 2000 bootstrap samples where the adjusted difference is estimated in each of the 2000 bootstrap samples and we define the 95% confidence interval (CI) to be the 2.5th and 97.5th centiles. In scenarios where we found evidence of a temporal trend, we assessed whether the outcome is different than predicted in the after implementation period given the trends before implementation. Using the multivariable models generated among the patients before implementation we generated a prediction for those treated in the after-implementation period. We then calculated the difference between the predicted values and the outcomes in the after-implementation period along with 95% confidence intervals (CIs) calculated by repeating the analysis using 2000 bootstrap samples. As the uptake of various aspects of compliance may have been gradual for all analyses outlined, we excluded patients treated ±1 month of the implementation of the protocol and as sensitivity analyses, we excluded patients treated ±3 months. All analyses were conducted using R 4.1.2.

Table 1
Patient Characteristics before versus after the implementation of the new anesthetic protocol using a ±1 month window. Data are presented as median (quartiles) or frequency (%).

Characteristics	Before implementation, $n = 4407$	After implementation, $n = 1331$	P-value[a]
Age (years)	51 (43, 61)	51 (43, 61)	0.5
Female	4326 (98.2%)	1311 (98.5%)	0.4
BMI (kg/m^2)	25 (22, 29)	26 (22, 30)	0.011
ASA score			< 0.001
1	52 (1.2%)	9 (0.7%)	
2	2562 (58.1%)	703 (52.8%)	
3	1790 (40.6%)	615 (46.2%)	
4	3 (< 0.1%)	4 (0.3%)	
Apfel score			0.2
0–2	341 (7.7%)	85 (6.4%)	
3	3137 (71.2%)	951 (71.5%)	
4	929 (21.1%)	295 (22.2%)	
Outpatient surgery	14 (0.3%)	14 (1.1%)	< 0.001
Overnight stay	4300 (97.6%)	1302 (97.8%)	0.3
Unknown	0	3	
Intraoperative antiemetic	4211 (95.6%)	1257 (94.4%)	0.093
Block	2812 (63.8%)	885 (66.5%)	0.073
Anesthetic time (in min)	220 (180, 261)	221 (178, 261)	> 0.9
Operative time (in min)	169 (131, 207)	169 (129, 207)	0.6
Bilateral procedure	2251 (51.1%)	672 (50.5%)	0.7
Reconstruction	3173 (72.0%)	918 (69.0%)	0.032

[a] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

Results

There were 5902 qualifying surgeries corresponding to 5853 unique patients at the Josie Robertson Surgery Center from January 2016 through September 2021. We excluded 49 patients' second surgeries. A total of 244 patients had a reoperation and of those 196 (80.3%) had a reoperation due to hematoma. Characteristics for all procedures were compared by study period in Table 1. Rates of reconstruction were significantly lower in the after-implementation period using either window (72% vs 69%; $P \leq 0.032$; Table 1). Median BMI was 1 unit higher among those treated in the post-implementation period using either window ($P \leq 0.027$; Table 1). Although the association was not significant, the rate of intraoperative antiemetics was slightly lower among patients treated after implementation (96% vs 94%; $P = 0.093$; Table 1).

Table 2 provides all of the components of the ERP as well as the rates of compliance before and after the protocol implementation. Most notable is the increase in TIVA compliance which increased by 17% (95% CI, 14%, 20%; $P < 0.001$). In addition, rates of peripherial nerve block (PNB), dexamethasone, and acetaminophen were statistically significantly higher after implementation (Table 2). We did not have sufficient evidence of a difference in gabapentin or ondansetron however the rates before implementation were extremely high (Table 2). Although not an element of the updated protocol, the use of surgeon-administered local anesthetic decreased significantly after implementation ($P < 0.001$). The use of intraoperative ketorolac dropped from 44% to nearly no utilization (0.7%) after implementation ($P < 0.001$). The amount of postoperative opioids consumed in Morphine equivalent dose (MME) decreased from a median (quartiles) of 18 (6, 32) to 12 (4, 26), corresponding to a difference in means of 4.4 MME (95% CI, 3.2, 5.6; $P < 0.001$). When assessing compliance using a three-month window we exclude one additional patient who received ketorolac nearly three months after implementation.

Table 2

Compliance with protocol elements before and after implementation of the new anesthetic protocol using a ±1 month window. Summary statistics are presented as median (quartiles) or frequency (%). Differences are presented as the after implementation period subtracted from the before implementation period and presented as mean or absolute difference with corresponding 95% confidence intervals.

Characteristic	Before implementation, $n = 4407$	After implementation, $n = 1331$	Difference[a]	95% CI[ab]	P-value[a]
Intraoperative opioids (MME)	30 (20, 40)	30 (20, 40)	4.7	3.8, 5.6	< 0.001
Postoperative opioids (MME)	18 (6, 32)	12 (4, 26)	4.4	3.2, 5.6	< 0.001
Total MME	50 (35, 71)	42 (28, 60)	9.1	7.5, 11	< 0.001
Intraoperative local anesthetic	558 (12.7%)	57 (4.3%)	8.4%	6.9%, 9.9%	< 0.001
Intraoperative ketorolac	1920 (43.6%)	9 (0.7%)	43%	41%, 44%	< 0.001
Received PNB	2793 (63.4%)	875 (65.7%)	−7.2%	−9.3%, −5.1%	< 0.001
Unknown	1148	389			
Received gabapentin	3377 (76.6%)	1002 (75.3%)	−0.45%	−2.1%, 1.2%	0.6
Unknown	797	265			
Received dexamethasone	4228 (95.9%)	1305 (98.0%)	−2.1%	−3.1%, −1.1%	< 0.001
Received ondansetron	4210 (95.5%)	1261 (94.7%)	0.79%	−0.61%, 2.2%	0.3
Received acetaminophen	4160 (94.4%)	1311 (98.5%)	−4.1%	−5.1%, −3.1%	< 0.001
TIVA	1529 (34.7%)	691 (51.9%)	−17%	−20%, −14%	< 0.001

[a] Welch two sample t-test; two sample test for equality of proportions.
[b] CI = Confidence interval.

Table 3

Outcomes by before and after implementation presented as frequency (%). Absolute differences are presented as the after implementation period subtracted from the before implementation period with corresponding 95% confidence intervals.

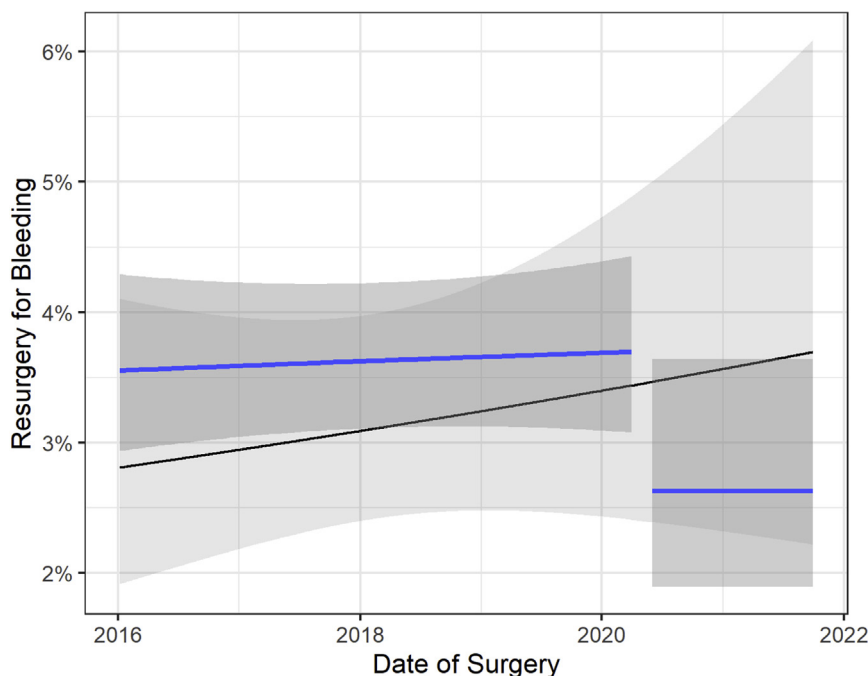| Group	Characteristics	Before implementation, $n = 4407$	After implementation, $n = 1331$	Difference	95% CI[12]
Excluding ± 1 month	Reoperation due to bleeding	160 (3.6%)	35 (2.6%)	1.0%	−0.07%, 2.1%
	PONV rescue	1149 (26.1%)	261 (19.6%)	6.5%	3.9%, 9.0%
Excluding ± 3 months	Reoperation due to bleeding	154 (3.5%)	29 (2.2%)	1.2%	0.1%, 2.3%
	PONV rescue	1115 (25.3%)	234 (17.6%)	6.7%	4.0%, 9.3%

[2] CI = Confidence interval

Fig. 1. Probability of reoperation due to hematoma formation estimated using multivariable logistic regression using patients who underwent surgery on or prior to March 31, 2020 projected onto surgeries occurring on or after June 1, 2020 (black line). The model adjusted for surgery date, age, BMI, bilateral surgery, reconstruction procedure, use of antiplatelet and use of an anticoagulant and the estimates were generated for the average patient. The blue lines represent generalized additive models generated separately for those who underwent. Surgery on or prior to March 31, 2020 and after June 1, 2020. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Rates of the outcomes by study periods are displayed in Table 3. To assess whether the elimination of ketorolac was associated with the expected outcome of decreased reoperation due to bleeding, we performed a multivariable analysis utilizing the same covariates as the previous analysis.[10] The rate of reoperation due to bleeding decreased from 3.6% to 2.6% after implementation however, after adjusting for age, BMI, bilateral surgery, reconstruction procedure, use of antiplatelet and use of an anticoagulant did not meet conventional levels of significance (OR = 0.69; 95% CI, 0.47, 0.99; $P = 0.053$). The adjusted decrease associated with being treated in the after implementation period was 1.0% (bootstrap 95% CI, 0.11%, 1.9%). Results excluding ± three months were nearly identical but, in this comparison, differences between groups were statistically significant (OR = 0.64; 95% CI, 0.42, 0.94; $P = 0.028$) with an adjusted decrease being 1.2% (bootstrap 95% CI 0.2%, 2.0%). Although the association between the probability of reoperation due to hematoma formation and surgery date was not statistically significant (P
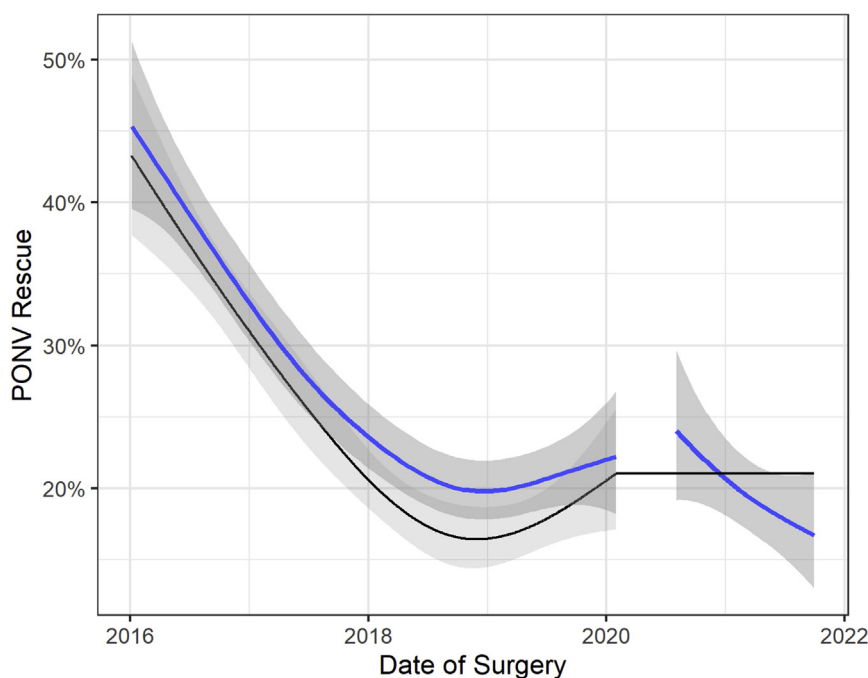
Fig. 2. Probability of requiring PONV rescue estimated using multivariable logistic regression among patients who underwent surgery on or prior to March 31, 2020 projected onto surgeries occurring on or after June 1, 2020 (black line). The model included cubic splines for surgery date and adjusted for consumed with estimates age and Apfel score and the estimates were generated for the average patient. The blue lines represent generalized additive models generated separately for those who underwent surgery on or prior to March 31, 2020 and after June 1, 2020. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
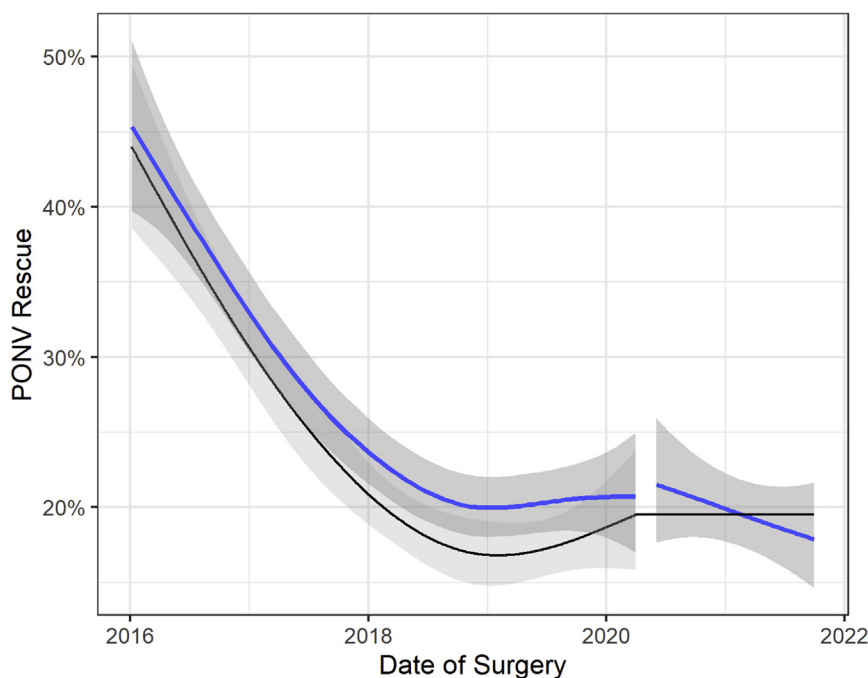

Fig. 3. Probability of requiring PONV rescue estimated using multivariable logistic regression among patients who underwent surgery on or prior to January 31, 2020 projected onto surgeries occurring on or after August 1, 2020 (black line). The model included cubic splines for surgery date and adjusted for consumed with estimates age and Apfel score and the estimates were generated for the average patient. The blue lines represent generalized additive models generated separately for those who underwent surgery on or prior to January 31, 2020 and after August 1, 2020. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

= 0.5), we performed a sensitivity analysis using the projection method outlined in the methods section. The rate of reoperation due to hematoma formation was 1.0% (bootstrap 95% CI, -0.5%, 3.2%) lower than expected in the after-implementation period excluding ± 1 month (Fig. 1). In terms of the other covariates, on multivariable analysis excluding the 1-month window reconstruction was the only other predictor of a reduction in the risk reoperation due to hematoma formation (OR = 0.52; 95% CI, 0.38, 0.73; $P < 0.001$). For the sensitivity analysis excluding a 3-month window the reduction associated with reconstruction was nearly identical (OR = 0.53; 95% CI, 0.38, 0.75; $P < 0.001$) additionally, higher BMI was significantly associated with a higher risk of

reoperation due to hematoma formation (OR = 1.03; 95% CI, 1.00, 1.05; $P = 0.037$).

Prior to the updated protocol implementation, the rates of PONV had already improved since the beginning of our data collection; at the opening of JRSC, January 2016, our rates were 45% and decreased to 20% in January 2019. For both the primary (±1 month) and sensitivity (±3 months) (Table 3) analyses, the association between the risk of requiring PONV rescue medication and the date of surgery (plus cubic splines) was significant on multivariable logistic regression analysis among patients treated before implementation after adjusting for total amount of opioids ($P < 0.001$ and $P < 0.001$, respectively). In the after-

implementation period excluding ± 1 month the rate of requiring rescue medication for PONV was -0.10% (bootstrap 95% CI, -4.6%, 4.5%) (Fig. 2) lower than expected and results were similar excluding ± 3 months with the rate being 1.3% (bootstrap 95% CI, -3.3%, 6.1%) lower than expected (Fig. 3).

Discussion

Enhanced recovery protocols ideally involve ongoing data collection, the creation of updated guidelines to continue to improve patient outcomes, and the reassessment of the impact of these protocol changes on patient outcomes. Based on the current literature and our own internal studies, we encouraged the use of TIVA and removed ketorolac as part of standard of care for patients undergoing total breast mastectomy. We found high compliance with this protocol, leading to reduced risk of reoperation for hematoma although no change in the risk of PONV.

The current literature demonstrates that enhanced recovery protocols require interventions to improve adherence in order to improve outcomes.[11–13] The protocol was initially presented at a staff meeting for the anesthesia department, distributed in paper form to the operating rooms, and sent out via email. After the starting date, a team reviewed compliance to the protocol and sent email reminders to members of the anesthesia team involved in a case that did not follow the updated protocol. The results of the current study demonstrated a high rate of compliance with the new protocol and in particular a significant increase in TIVA administration and a decrease in ketorolac administration.[14] Thus, our process of disseminating information, assessing compliance, and sending reminders was an effective method of quality improvement and can serve as a model for other enhanced recovery protocols.

Our current study assessed whether practice changes had the expected results on patient outcomes. As a previous study demonstrated that ketorolac was a risk factor of hematomas requiring reoperation, we eliminated the administration from the protocol and evaluated whether the rates of reoperation decreased.[10] We demonstrated it is feasible to remove ketorolac as part of standard of care and our rates of administration dropped to near zero. We demonstrated a significant decrease in the rate of reoperation due to hematoma formation based on the ± 3 month window and the adjusted difference estimate was similar for the ± 1 month window but did not meet conventional levels of significance.

Overall, the rate of reoperation due to hematoma formation was low to begin with and based on the primary analysis our confidence interval includes up to a 1.9% decrease in the after implementation period which translates to one fewer reoperation due to hematoma formation for every 53 patients. While it is possible that other aspects of the protocol changes may explain part of the decrease in the rate of reoperation due to hematoma formation it is highly likely this change is driven by the elimination of ketorolac. The previous study[10] demonstrated over a 2-fold increase in the risk of reoperation due to hematoma formation associated with ketorolac after adjusting for other known risk factors of hematoma formation and our analysis adjusted for the same set of predictors. None of the other protocol element changes are not known risk factors for hematoma formation. Indeed, we believe that the findings reported here confirms that the association we previously reported was causal.

Our second patient relevant outcome was PONV. Patients at high risk for PONV require a multifaceted approach to reduce the risk of nausea.[6,15] The published literature reports up to 35% of women undergoing breast cancer surgery experience PONV after surgery even with intraoperative antiemetic administration,[16] which reflects the initial rates of PONV (45%) we witnessed in this population but were able to decrease to 26% by January 2019 (Fig. 3). We already had a high rate of intraoperative antiemetic usage due to the initial protocol (96%) and needed to include additional interventions to further decrease the rates of PONV within the population. The initial mastectomy protocol led to an increase in TIVA usage by 28% (95% CI, 20–40).[2] However, despite the known benefits of TIVA, anesthesia providers describe being hesitant to

use the technique due to reasons such as an increased setup time, risk of missing drug delivery, and lack of real-time monitoring of propofol concentration.[17] Our study demonstrated a large increase of TIVA usage following the protocol updates.

Limitations of our study include the single institution approach. The protocol was multifaceted, introducing several different changes simultaneously thereby making it difficult to ascertain which specific elements caused the changes in outcomes. The rate of all hematomas, including those that did not require a surgery, is higher than we reported. However, we have no reason to suspect that the association between surgery period and any hematoma would be inconsistent with the association between surgery period and a hematoma requiring surgery.

In addition to changes in compliance, we demonstrate significant differences in a few measured confounders. Patients treated postimplementation tended to have higher BMI and were less likely to receive reconstruction, we have evidence that both are risk factors for requiring a reoperation due to hematoma. As such, if there is any bias related to unmeasured confounding biased towards the null hypothesis of no effect of the protocol. Yet we still found evidence that the protocol reduced reoperation. The other covariates were not significantly associated with the outcome. The rates of reoperation and PONV were also already low and we did not have enough power to detect significant differences in such small changes.

Conclusions

Enhanced recovery protocols should be dynamic processes that utilize internal data and evidence-based practice to continually improve the patient experience. Although compliance with many of the elements of the protocol elements was already high before implementation, we were able to improve compliance and patient outcomes for nearly all components after protocol implementation with the use of effective feedback, communication, and teamwork translating to meaningful change in patient outcomes. The development and implementation of an updated protocol for patients undergoing total breast mastectomies led to a drastic increase in TIVA usage, near elimination of ketorolac, and a decrease in reoperation due to hematoma formation.

Funding

Declaration of competing interest

None declared.

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