Can J Anesth/J Can Anesth (2022) 69:1477–1492
https://doi.org/10.1007/s12630-022-02336-8

REPORTS OF ORIGINAL INVESTIGATIONS

Opioid-sparing anesthesia and patient-reported outcomes after open gynecologic surgery: a historical cohort study

Anesthésie avec épargne opioïde et issues rapportées par les patientes après une chirurgie gynécologique avec laparotomie : une étude de cohorte historique

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Received: 1 November 2021 / Revised: 13 April 2022 / Accepted: 30 May 2022 / Published online: 12 October 2022

Abstract

Purpose *Dexmedetomidine and ketamine may be administered intraoperatively as continuous infusions to provide opioid-sparing anesthesia. Recent evidence has yielded controversial results regarding the impact of opioid-free anesthesia on postoperative complications, and there is a gap in knowledge regarding patient-reported outcomes (PROs). This study aimed to determine the impact of opioid-sparing anesthesia and opioid-based anesthesia on PROs among gynecologic patients within an enhanced recovery after surgery (ERAS) program.*

Methods *We formed a single-center historical cohort from patients enrolled in another study who underwent open gynecologic surgery on an ERAS program from November 2014 to December 2020 (n = 2,095). We identified two cohorts based on the type of balanced anesthesia administered: 1) opioid-sparing anesthesia defined as the continuous infusion of dexmedetomidine and ketamine (adjuvants) during surgery or 2) opioid-based anesthesia (no adjuvants). We measured the quality of postoperative recovery using the MD Anderson Symptom Inventory (MDASI), a 29-item validated tool that was administered preoperatively, daily while admitted, and weekly after discharge until week 6. The primary outcome was interference with walking. We matched both cohorts and used a multilevel linear mixed-effect model to evaluate the effect of opioid-sparing anesthesia on the primary outcome.*

Results *In total, 498 patients were eligible (159 in the opioid-sparing anesthesia cohort and 339 in the opioid-based anesthesia cohort), of whom 149 matched pairs were included in the final analysis. Longitudinal assessment*

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12630-022-02336-8.

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showed no significant or clinically important difference in interference with walking (P = 0.99), general activity (P = 0.99), or other PROs between cohorts. Median [interquartile range (IQR)] intraoperative opioid administration (expressed as morphine milligram equivalents [MME]) among matched patients in the opioid-sparing anesthesia cohort was 30 [25–55] mg vs 58 [8–70] mg in the opioid-based anesthesia cohort (P < 0.01). Patients in the opioid-sparing anesthesia cohort had a lower opioid consumption in the postanesthesia care unit than those in the opioid-based anesthesia cohort (MME, 3 [0–10] mg vs 5 [0–15] mg; P < 0.01), but there was no significant difference between cohorts in total postoperative opioid consumption (MME, 23 [0–94] mg vs 35 [13–95] mg P = 0.053).

Conclusions *In this single-center historical cohort study, opioid-sparing anesthesia had no significant or clinically important effects on interference with walking or other PROs in patients undergoing gynecologic surgery compared with opioid-based anesthesia. Opioid-sparing anesthesia was associated with less short-term opioid consumption than opioid-based anesthesia.*

Résumé

Objectif *La dexmédétomidine et la kétamine peuvent être administrées en peropératoire sous forme de perfusions continues pour fournir une anesthésie avec épargne opioïde. Des données probantes récentes ont présenté des résultats controversés concernant l'impact d'une anesthésie sans opioïdes sur les complications postopératoires, et il existe une lacune dans les connaissances concernant les issues rapportées par les patients (IRP). Cette étude visait à déterminer l'impact d'une anesthésie avec épargne opioïde et d'une anesthésie à base d'opioïdes sur les IRP chez les patientes de chirurgie gynécologique dans le cadre d'un programme de Récupération rapide après la chirurgie (ERAS – Enhanced Recovery After Surgery).*

Méthode *Nous avons formé une cohorte historique monocentrique composée de patientes inscrites à une autre étude qui ont bénéficié d'une chirurgie gynécologique avec laparotomie dans le cadre d'un programme d'ERAS entre novembre 2014 et décembre 2020 (n = 2095). Nous avons identifié deux cohortes en fonction du type d'anesthésie équilibrée administrée : 1) anesthésie avec épargne opioïde, définie comme une perfusion continue de dexmédétomidine et de kétamine (adjuvants) pendant la chirurgie, ou 2) anesthésie à base d'opioïdes (sans adjuvants). Nous avons mesuré la qualité de la récupération postopératoire à l'aide de l'inventaire des symptômes MDASI, un outil validé comportant 29 éléments qui a été administré avant l'opération, quotidiennement pendant l'admission et chaque semaine après le congé jusqu'à la semaine 6. Le critère d'évaluation principal était l'interférence avec la marche. Nous avons apparié les deux cohortes et utilisé un modèle linéaire à effets mixtes à plusieurs niveaux pour évaluer l'effet de l'anesthésie avec épargne opioïde sur le critère d'évaluation principal.*

Résultats *Au total, 498 patientes étaient éligibles (159 dans la cohorte d'anesthésie avec épargne opioïde et 339 dans la cohorte d'anesthésie à base d'opioïdes), dont 149 paires appariées ont été incluses dans l'analyse finale. L'évaluation longitudinale n'a révélé aucune différence significative ou cliniquement importante dans l'interférence avec la marche (P = 0,99), l'activité générale (P = 0,99), ou d'autres IRP entre les deux cohortes. L'administration médiane d'opioïdes peropératoires [écart interquartile (ÉIQ)] (exprimée en équivalents de morphine en milligrammes [EMM]) chez les patientes appariées de la cohorte d'anesthésie avec épargne opioïde était de 30 [25-55] mg vs 58 [8–70] mg dans la cohorte d'anesthésie à base d'opioïdes (P < 0,01). Les patientes de la cohorte d'anesthésie avec épargne opioïde avaient une consommation d'opioïdes plus faible en salle de réveil que celles de la cohorte d'anesthésie à base d'opioïdes (EMM, 3 [0-10] mg vs 5 [0–15] mg; P < 0,01), mais il n'y avait pas de différence significative entre les cohortes dans la consommation totale d'opioïdes postopératoires (EMM, 23 [0-94] mg vs 35 [13–95] mg; P = 0,053).*

Conclusion *Dans cette étude de cohorte historique monocentrique, l'anesthésie avec épargne opioïde n'a eu aucun effet significatif ou cliniquement important sur l'interférence avec la marche ou d'autres IRP chez les patientes bénéficiant d'une chirurgie gynécologique par rapport à l'anesthésie à base d'opioïdes. L'anesthésie avec épargne opioïde était associée à une consommation d'opioïdes moindre à court terme que l'anesthésie à base d'opioïdes.*

Keywords anesthesia · enhanced recovery · enhanced recovery after surgery · gynecologic surgery · patient-reported outcomes · perioperative medicine

Pain management during surgery is a key component of perioperative anesthetic care, and routine intervention for perioperative pain management is focused on opioid administration.[1] Nevertheless, excessive intraoperative opioid use has been associated with increased postoperative morbidity and opioid-related adverse drug events (ORADEs) including ileus, nausea and vomiting, respiratory depression, prolonged length of hospital stay, and higher rates of readmission.[2] In addition, the current

opioid crisis in the USA has reached alarming rates of overdose-related deaths along with substantial increases in opioid addiction, misuse, diversion, and abuse,[3] all of which are frequently preceded by opioid overprescribing practice during hospital admissions and at discharge for elective surgical procedures.[4,5] In light of this risk, the Enhanced Recovery After Surgery (ERAS®) Society has compiled a set of evidence-based guidelines that emphasize the importance of opioid-sparing analgesic regimens and raise awareness about opioid stewardship among healthcare providers.[6,7] Unfortunately, despite these recommendations, opioids are still the most commonly used medication for intraoperative analgesia as well as a cornerstone for postoperative analgesia.[8]

Recently, there has been increasing interest on opioid-free anesthesia, which is based on the use of multimodal intravenous anesthesia encompassing the combination of multiple synergistic analgesic agents acting on different nociceptive pathways.[9] Some ERAS protocols have proposed the combination of intravenous opioid-sparing anesthetics,[10] such as dexmedetomidine and ketamine, which in combination may accelerate recovery because of their postoperative analgesic properties.[11] Although both of these agents have become increasingly popular as an alternative to spare intraoperative opioid administration and to reduce perioperative pain, a recent multicentric trial showed that opioid-free anesthesia based on dexmedetomidine, ketamine, and lidocaine increases serious adverse events (e.g., postoperative hypoxemia) and does not provide clinically significant short-term benefits (better postoperative pain control and fewer ORADEs).[12] Moreover, according to the Perioperative Quality Initiative workgroup, there is a gap in knowledge pertaining to clinically meaningful patient-reported outcomes (PROs) with regards to anesthetic techniques.[13,14] Therefore, we hypothesized that multimodal, opioid-sparing anesthesia may impact quality of recovery as measured by PROs compared with opioid-based anesthesia.[15] Our primary outcome was interference with walking as this is an indicator of recovery that has shown to provide valuable information about performance status, symptom severity/burden, and physical well-being/functioning throughout the postoperative period.[16,17] We focused this hypothesis in patients undergoing gynecologic oncology surgery because this patient population has a high degree of morbidity and experiences a significant burden on quality of life in the postoperative period.[18]

Our primary objective was to compare PROs between a multimodal nonopioid anesthetic regimen composed of dexmedetomidine and ketamine infusions *vs* opioid-based anesthesia in patients undergoing open gynecologic surgery within an ERAS program.

Methods

Study design and participants

We conducted a historical cohort study including patients who underwent open gynecologic surgery within the ERAS program between November 2014 and March 2020. Our institutional review board approved the protocol (PA21-0196). Written informed consent was not required because of the retrospective nature of the study. All PROs were collected for other studies under separate institutional review board-approved protocols (BS99-094, 2017–0412, and 2018– 0143) and it was not part of usual care in our institution. The objectives of those studies were to evaluate the MD Anderson Symptom Inventory (MDASI) questionnaire[A] as an instrument to estimate functional status and to assess its impact on quality of life. Inclusion criteria were adult patients being followed at the MD Anderson Cancer Center and undergoing open surgery for gynecologic cancer or benign tumors. Exclusion criteria included inability to provide informed consent, refusal to participate, and inability to complete the survey because of poor performance status. Written informed consent for PRO collection and study participation was obtained from all participants. Patients were enrolled in the ERAS program for gynecology oncology and all of them were formally invited to participate in the PRO survey. The original cohort of this protocol comprised patients in the ERAS program who accepted the invitation.

Inclusion and exclusion criteria

We included adults $\geq$ 18 yr of age who underwent open gynecologic surgery, were English speaking, and had completed at least three timepoints for PROs (including the baseline preoperative MDASI questionnaire[19] and two subsequent assessments). We excluded patients who underwent emergency surgery, those undergoing multidisciplinary procedures, or those undergoing reoperations during same admission. Chronic opioid use (see below) was not considered an exclusion criterion for this analysis.

Anesthetic care

All patients in the ERAS program received standardized multimodal analgesia preoperatively (acetaminophen, pregabalin, celecoxib, and tramadol) per protocol unless

[A] *The MD Anderson Symptom Inventory*. Available from URL: https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools/md-anderson-symptom-inventory.html (accessed June 2022)

contraindicated. All ERAS elements are listed in Electronic Supplementary Material (ESM) eTable 1. In our institution, each anesthesiologist chooses the anesthetic plan based on individual patient characteristics, comorbidities, and clinical experience. At the end of surgery, patients received wound infiltration with liposomal bupivacaine or plain bupivacaine (various patients of this analysis were previously enrolled in a randomized trial comparing the two approaches).[20] For this study, there was no documentation about the type of local anesthetic used, but previous evidence has shown no significant analgesic difference between both local anesthetics.[20] None of the patients in this cohort received a transversus abdominis plane block or an erector spinae plane block. In our institution, the use of epidurals is very rare. Each anesthesiologist administered opioids intraoperatively based upon their own experience considering the sympathetic response to surgical stimuli. Nevertheless, some anesthesiologists in our institution routinely administer opioid-sparing anesthesia with dexmedetomidine and ketamine, providing an opportunity to study its effects.

For the purpose of the final analysis, we categorized patients into two cohorts based on the type of anesthesia: 1) opioid-sparing anesthesia was defined as the concomitant use of dexmedetomidine (0.3–1.0 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) and ketamine infusions (5.0–7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during surgery and 2) opioid-based anesthesia was defined as maintenance of analgesia exclusively through the use of fentanyl throughout surgery. None of the patients received lidocaine infusions intraoperatively or postoperatively. We matched both cohorts using propensity scores that included variables with significant unbalance in univariate analysis as well as biological correlation with our primary outcomes.

Covariates

Demographics (age, race, body mass index), surgical characteristics (duration of surgery, surgical complexity),[21] and comorbidities (American Society of Anesthesiologists [ASA] Physical Status, chronic obstructive pulmonary disease [COPD], hypertension, coronary artery disease, chronic opioid use, and psychiatric disease) were used as covariates in this study. Preoperative opioid use was also extracted and defined as exposure to opioids within 30 days before surgery. Chronic opioid use was defined as opioid consumption for more than 30 days before surgery. Total opioid consumption after surgery was measured as the morphine equivalent dose in mg (morphine milligram equivalents, MME),[22] which included the amount of opioid consumed after surgery including in the postanesthesia care unit (PACU) and inpatient unit. Compliance with ERAS was calculated as the percentage of ERAS items (see ESM eTable 1) that were successfully applied in each case. These data were extracted retrospectively from medical records and collected using Research Electronic Data Capture (REDCap; Vanderbilt University; Nashville, TN, USA) tools.[23]

Outcomes

The outcomes of this study were primarily based on the MDASI, which was previously published and validated.[18] Outcomes were measured at baseline, daily while admitted postoperatively, on days 3 and 7 after hospital discharge, and weekly for six weeks after discharge. All PROs for this study were collected under a standardized protocol using a validated 27-item tool.[19] Our main PROs included interference with walking, general activity, mood, working, relationship, and enjoyment, as well as patient-reported pain scores, nausea, vomiting, constipation, fatigue, attention, memory, and drowsiness. For each symptom component, individuals were asked to rank symptom severity at its worst during the previous 24 hr on a scale of 0–10, with 0 being "not present" and 10 being "as bad as you can imagine." Symptom interference was also assessed on a 0–10 scale, with 0 being "did not interfere" and 10 being "interfered completely." Interference scores were measured for general activity, mood, work (including work around the house), relations with other people, walking, and enjoyment of life. The PRO survey was filled in a paper form while in the hospital and then electronically after hospital discharge.

In this study, the primary outcome was interference with walking, which has been shown to be a fundamental indicator of postoperative recovery, to be associated with the prevention of potential complications (e.g., thrombosis, ileus, pain), and to be a facilitator for early hospital discharge.[24]

Secondary clinical outcomes included postoperative complications based on electronic medical records, including cardiac, respiratory, gastrointestinal, and renal complications within 30 days after surgery. Acute kidney injury (AKI) was classified according to the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria[25] as follows: *risk* (increased serum creatinine 1.5 times or urinary output $< 0.5\ mL \cdot kg^{-1} \cdot hr^{-1}$ for six hours), *injury* (increased serum creatinine two times or urinary output $< 0.5\ mL \cdot kg^{-1} \cdot hr^{-1}$ for 12 hr), and *failure* (increased serum creatinine three times or urinary output $< 0.3\ mL \cdot kg^{-1} \cdot hr^{-1}$ or anuria for 24 hr). We also abstracted intraoperative opioid administration, and postoperative opioid consumption in the PACU as well as throughout the hospital stay from postoperative day (POD) 1 to POD 5.

Statistical analysis

Both quantitative and qualitative variables are represented using means with standard deviations (SDs) or medians with interquartile ranges [IQRs] depending on the distribution of the data. We compared clinical and sociodemographic data with the Shapiro–Wilk test. We categorized patients *a priori* into two cohorts based on the anesthesia technique (opioid-sparing anesthesia defined as the concomitant use of dexmedetomidine and ketamine infusions, and opioid-based anesthesia with no intravenous adjuvants). We conducted univariate analyses to compare demographic and clinical characteristics between both cohorts. For comparisons of quantitative variables, we used the one-sided Student's *t* test or Mann–Whitney U test based on the distribution of the data. For categorical variables, we used the Chi square test (when there were more than ten events in either group) or Fisher's exact test (when there were less than or equal to ten events in either group) to compare categorical variables between the opioid-based and opioid-sparing cohorts. Sample size was determined by convenience based on availability of patients from the original studies. As a reference, for a minimally important difference of 30% of the primary outcome, which is equivalent to half of the SD of interference with walking −1.5 points in the primary outcome from 5 points to 3.5 points, a total sample size of 502 patients would be required to achieve 80% power and a type I error of 5%.

Propensity scores for each patient were obtained using binomial logistic regressions. The model followed standard recommendations for matching cohort analysis in anesthesia, considering the following criteria: 1) preoperative variables, 2) evidence of confounding bias (statistical significance in univariate analysis), or 3) biological correlation with our primary outcomes. In this study, the variables included in the propensity score model were age, chronic opioid use, and preoperative multimodal analgesia (for more details, see ESM eTable 2). Patients were matched (1:1) using the nearest neighbor method (greedy technique) without replacement and a caliper of 0.05 of the SD of the logit of the estimated propensity score. We initially compared short-term PROs during hospitalization using a longitudinal mixed-effect model to adjust for multiplicity (timepoints). Postdischarge PRO data were analyzed longitudinally from week 2 until week 7 using multilevel linear mixed-effects models to assess the impact of anesthesia technique on PROs. Our model considered intercepts (fixed-effects parameters) by timepoint of assessment and patient identification number, as well as fixed-effects parameters including type of anesthesia (opioid-sparing *vs* opioid-based anesthesia) year of surgery, and compliance with ERAS protocol. We adjusted the results for multiple endpoints using Holm–Bonferroni correction. Additionally, we plotted these trends with their corresponding 95% confidence interval for each PRO assessed daily from POD 0 until POD 7, as well as postdischarge from week 2 to week 7. We performed a sensitivity analysis to distinguish the effect of opioid-sparing anesthesia based on compliance with ERAS ($\geq$ 80% considered high compliance *vs* $<$ 80% low compliance). We considered a *P* value less than 0.05 statistically significant. All analyses were performed in Stata 14.0 (StataCorp LLC, College Station, TX, USA).

Results

Patient characteristics

Out of 2,095 patients enrolled in the ERAS cohort, we initially excluded 1,009 patients who did not complete PROs due to lack of consent, 192 who received ketamine alone, and 154 who received dexmedetomidine alone. After excluding 208 patients who withdrew from the original studies and 34 patients with incomplete PROs, we obtained a total sample size of 498 patients (Fig. 1). Baseline characteristics were similar between the group of patients who consented for PROs *vs* those who did not consent (median [IQR] age, 58 [47–67] yr *vs* 59 [48–67] yr; $P = 0.40$; ASA Physical Status $\geq$ III, 89% *vs* 92%; $P = 0.20$; high compliance with ERAS, 38% *vs* 43%; $P = 0.06$).

In total, 498 patients were eligible, 159 of whom received a multimodal opioid-sparing anesthetic regimen (dexmedetomidine and ketamine) and 339 of whom received opioid-based anesthesia. Most patients had an ASA Physical Status score of III/IV (456/498, 92.5%), the median [IQR] age was 59 [48–67] yr, and 94% were opioid-naïve patients. In the unmatched cohort, patients who received opioid-sparing anesthesia were younger (56 [48–64] yr *vs* 60 [48–68] yr, $P = 0.02$), had longer surgical procedures (234 [183–300] min *vs* 212 [167–272] min, $P = 0.01$), and a greater proportion received preoperative celecoxib (92.9% *vs* 85.5%, $P = 0.02$) compared with those in the opioid-based anesthesia cohort (Table 1). After propensity score matching, there were a total of 149 matched pairs with comparable demographics and clinical characteristics (Table 2). Balance was confirmed (ESM eFigs. 1 and 2) and the percentage of bias reduced from 11.4% to 3.4%. The surgical approach, duration of surgery, and perioperative multimodal analgesia were similar between the cohorts. The opioid-sparing anesthesia cohort received dexmedetomidine at a dose of 0.3–1.0 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ and ketamine at a dose of 5.0–7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during surgery. None of the patients

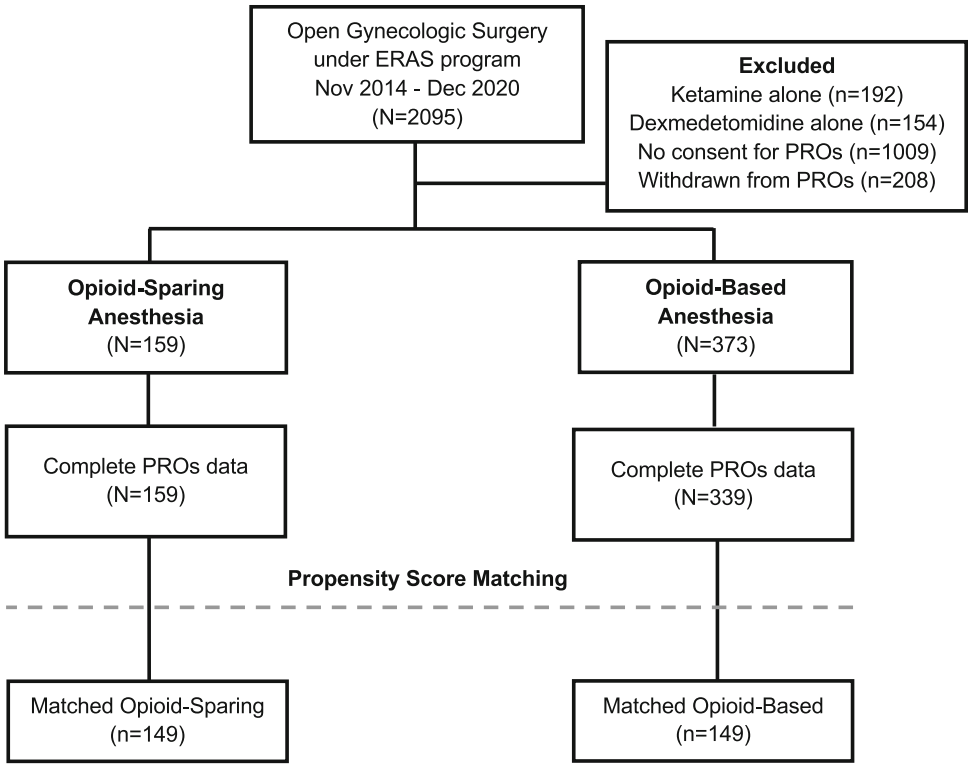

Fig. 1 Flowchart of patient selection

received lidocaine infusions intraoperatively or postoperatively. In terms of opioid administration during surgery, patients in the opioid-sparing anesthesia cohort received a mean [IQR] MME of 30 [25–55] mg and patients in the opioid-based anesthesia cohort 58 [38–70] mg ($P < 0.01$; Table 3). The median follow-up time in the matched cohort was until week 4 and the completion rates varied as shown in ESM eTable 3.

Primary outcome: interference with walking

Within the matched cohort, 2,467 observations corresponded to interference with walking (884 during hospitalization and 1,583 after hospital discharge). Both cohorts had similar interference with walking during hospitalization ($P = 0.99$, Table 4) and after hospital discharge ($P = 0.99$, Table 4). Figure 2 shows the longitudinal trend of the interference with walking and general activity between opioid-sparing anesthesia and opioid-based anesthesia cohorts. Among patients with high compliance with ERAS ($\geq 80\%$), there were no significant differences between the cohorts in terms of interference with walking ($P = 0.78$ while in the hospital and $P = 0.65$ after hospital discharge). Similarly, in the subgroup of patients with low compliance with ERAS ($< 80\%$), interference with walking did not differ significantly between both cohorts ($P = 0.60$ while in the hospital and $P = 0.62$ after discharge).

In-hospital patient-reported secondary outcomes

There were 882 observations corresponding to secondary PROs during hospitalization. After accounting for within-subject covariance and multiple comparisons during hospitalization, there were no differences in the level of pain ($P = 0.99$; Fig. 3), nausea ($P = 0.96$; Fig. 3), vomiting ($P = 0.96$), memory ($P = 0.99$), attention ($P = 0.99$), drowsiness ($P = 0.99$, Fig. 3), interference with walking ($P = 0.99$), or physical activity ($P = 0.99$) at any point during hospitalization (Table 4). Patients in the opioid-sparing anesthesia cohort had higher constipation levels of 0.99 points ($P = 0.02$) at POD 2 and 1.03 points ($P = 0.02$) at POD 3 compared with the opioid-based anesthesia cohort, although this fell below half a SD threshold conventionally used as a clinical minimally important difference for the MDASI.[26]

Other secondary outcomes: postoperative opioid consumption and complications

Opioid-sparing anesthesia was associated with lower median [IQR] opioid consumption in the PACU (MME, 3 [0–10] mg *vs* 5 [0–15] mg; $P < 0.01$). There was no significant difference in total postoperative opioid consumption (MME, 23 [0–94] mg *vs* 35 [13–95] mg; $P = 0.05$). Both cohorts had a similar length of hospital stay (3 [2–4] days *vs* 3 [2–4] days; $P = 0.73$) and 30-day

Table 1 Demographics and clinical characteristics of the unmatched cohort

Variable	Opioid-sparing anesthesia $N = 159$	Opioid-based anesthesia $N = 339$	P value
Age (yr)	56 [48–64]	60 [48–68]	0.02[a]
BMI ($kg \cdot m^{-2}$)	27.6 [24.1–32.5]	28.5 [24.1–34.6]	0.43[a]
Race			0.14[b]
White	122/159 (77%)	236/339 (70%)	0.10[b]
African-American	12/159 (8%)	45/339 (13%)	0.06[b]
Others	25/159 (16%)	58/339 (17%)	0.70[b]
ASA Physical Status			
II	11/159 (7%)	26/339 (8%)	0.78[b]
III	141/159 (90%)	299/339 (89%)	0.76[b]
IV	5/159 (3%)	11/339 (3%)	0.95[b]
Missing	2/159 (1%)	3/339 (1%)	0.68[c]
Charlson comorbidity index			
0	22/159 (14%)	29/339 (9%)	0.08[b]
1–2	58/159 (37%)	123/339 (36%)	0.97[b]
≥ 3	79/159 (50%)	187/339 (55%)	0.25[b]
Tumor type			
Benign	24/159 (15%)	73/339 (22%)	0.09[b]
Malignant	125/159 (80%)	249/339 (75%)	0.24[b]
Borderline	8/159 (5%)	11/339 (3%)	0.33[b]
None	2/159 (1%)	6/339 (2%)	0.68[b]
Indication for surgery*			
Cervical cancer	12/159 (11%)	16/339 (7%)	0.16[b]
Uterine (nonsarcoma)	23/159 (21%)	50/339 (22%)	0.72[b]
Fallopian, ovary, peritoneal	72/159 (65%)	148/339 (66%)	0.33[b]
Uterine (sarcoma)	2/159 (2%)	8/339 (4%)	0.30[c]
Other	2/159 (2%)	4/339 (2%)	1.00[c]
Missing	48/159 (30%)	113/339 (33%)	0.88[b]
Preoperative opioid use	10/159 (6%)	20/339 (6%)	0.87[b]
Chronic pain	20/159 (13%)	42/339 (12%)	0.95[b]
Prior chemotherapy	67/159 (42%)	136/339 (40%)	0.67[b]
Prior radiation	5/159 (3%)	9/339 (3%)	0.76[b]
Surgical complexity score*			
Low	50/159 (63%)	126/339 (77%)	0.02[b]
Intermediate	25/159 (32%)	34/339 (21%)	0.07[b]
High	4/159 (5%)	3/339 (2%)	0.22[c]
Operating time (min)	234 [183–300]	212 [167–272]	0.01[a]
Estimated blood loss (mL)	240 [120–400]	250 [125–500]	0.45[a]
LOS	3 [2–4]	3 [2–4]	0.55[a]
Intraoperative opioid (MME [mg])	56 [37–70]	33 [25–57]	< 0.01[a]
Postoperative opioid (MME [mg])	25 [0–107]	30 [10–82]	0.18[a]
PACU	3 [0–10]	5 [0–15]	< 0.01[a]
Floor	18 [0–98]	23 [0–70]	0.50[a]
Epidural	1/159 (1%)	2/339 (1%)	0.94[c]
Previous abdominal surgery	84/159 (53%)	175/339 (52%)	0.77[b]
Celecoxib	146/159 (93%)	288/339 (86%)	0.02[b]
Pregabalin	127/159 (81%)	254/339 (76%)	0.21[b]
Tramadol	136/159 (87%)	274/339 (81%)	0.26[b]

Table 1 continued

Variable	Opioid-sparing anesthesia*N* = 159	Opioid-based anesthesia*N* = 339	*P* value
IV acetaminophen	154/159 (97%)	324/339 (96%)	0.50[b]
Comorbidity			
Diabetes mellitus	135/159 (85%)	291/339 (86%)	0.78[b]
COPD	2/159 (1%)	4/339 (1%)	0.94[c]
Hypertension	61/159 (38%)	144/339 (43%)	0.39[b]
CKD	1/159 (1%)	10/339 (3%)	0.10[c]
Readmission	21/159 (13%)	36/339 (11%)	0.40[b]
Reoperation	7/159 (3%)	4/339 (4%)	0.63[b]
Intraoperative transfusion	9/159 (6%)	24/339 (7%)	0.55[b]

Numbers are medians [interquartile ranges] or *n*/total *N* (%)

ASA = American Society of Anesthesiologists; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; IV = intravenous; MME = morphine milligram equivalents; PACU = postanesthesia care unit

[*]Only includes cancer diagnoses

[a]Mann–Whitney U test

[b]Chi square test

[c]Fisher's exact test

readmission rates (12.1% *vs* 10.7%; $P = 0.72$). As shown in Table 3, the incidence of cardiac, respiratory, and gastrointestinal complications within 30 days after surgery did not vary significantly between both cohorts. Nevertheless, we observed a significantly higher incidence of AKI risk among patients who received opioid-sparing anesthesia compared with opioid-based anesthesia (4.7% *vs* 0.7%; $P = 0.03$). Notably, patients in the opioid-sparing anesthesia cohort were more likely to receive goal-directed fluid therapy (70.4% *vs* 33.2%; $P < 0.01$), but there were no significant differences in median [IQR] net fluid balance between both cohorts (1,380 [955–1,782] mL *vs* 1,255 [800–1742] mL; $P = 0.11$). There were no differences in intraoperative blood transfusion requirements between cohorts (Table 2). Out of 78 anesthesiologists who provided anesthesia for this cohort of patients, only 27 (34.6%) provided opioid-sparing anesthesia, one of whom contributed to 38% of the opioid-sparing cases, four of whom contributed to 19% of the cases, and the rest of whom contributed to the remaining 43% of the cases.

Postdischarge patient-reported secondary outcomes

A total of 1,481 observations corresponding to postdischarge PROs were included in this analysis. In longitudinal mixed-effect analysis of the matched cohort, there was no significant difference in postdischarge pain scores ($P = 0.97$; Fig. 3), interference with general activity ($P = 0.99$; Fig. 2), memory ($P = 0.99$), constipation ($P = 0.98$), and nausea ($P = 0.99$). Table 5 shows detailed results of the linear mixed-effects model analysis. Other PRO trends are illustrated in ESM eFigs. 3–7.

Sensitivity analysis

Among patients with high compliance with ERAS ($\geq$ 80%), there were no significant differences between the cohorts in terms of interference with working ($P = 0.97$ while in the hospital and $P = 0.95$ after hospital discharge), pain ($P = 0.98$ while in the hospital and $P = 0.99$ after hospital discharge), nausea ($P = 0.86$ while in the hospital and $P = 0.99$ after hospital discharge), and drowsiness ($P = 0.97$ while in the hospital and $P = 0.99$ after hospital discharge). In the subgroup of patients with low compliance with ERAS ($<$ 80%), opioid-sparing anesthesia was associated with less nausea by -1.13 points ($P = 0.02$) while in the hospital but no difference after hospital discharge ($P = 0.74$). There was no difference for the rest of PROs, including interference with walking ($P = 0.97$ while in the hospital and $P = 0.93$ after hospital discharge), pain ($P = 0.92$ while in the hospital and $P = 0.99$ after hospital discharge), and drowsiness ($P = 0.99$ while in the hospital and $P = 0.93$ after hospital discharge).

Discussion

In this single-centre historical cohort study, opioid-sparing anesthesia had no effect on interference with walking, general activity, or other PROs in patients undergoing

Table 2 Balance of baseline clinical characteristics in the matched cohort

Variable	Opioid-sparing anesthesia $N = 149$	Opioid-based anesthesia $N = 149$	P value	SMD
Age (yr)	57 [49–64]	57 [46–65]	0.64[a]	0.070
BMI ($kg \cdot m^{-2}$)	28.1 [24.1–32.5]	28.0 [23.7–34.2]	0.99[a]	0.014
ASA Physical Status				0.019
II	11/149 (8%)	11/149 (7%)	0.97[b]	
III	132/149 (90%)	135/149 (91%)	0.82[b]	
IV	4/149 (3%)	3/149 (2%)	0.69[c]	
Missing	2/149 (1%)	0/149 (0%)	0.16[c]	
Charlson comorbidity index				0.077
0	18/149 (12%)	20/149 (13%)	0.74[b]	
1–2	54/149 (36%)	58/149 (39%)	0.63[b]	
≥ 3	77/149 (52%)	71/149 (48%)	0.49[b]	
Diabetes mellitus	22/149 (15%)	18/149 (12%)	0.50[b]	0.079
Hypertension	60/149 (40%)	61/149 (41%)	0.91[b]	0.014
COPD	2/149 (1%)	0/149 (0%)	0.16[c]	0.164
CKD	1/149 (1%)	3/149 (2%)	0.31[c]	0.116
Preoperative opioid use	10/149 (7%)	13/149 (9%)	0.52[b]	0.075
Chronic pain	17/149 (11%)	18/149 (12%)	0.86[b]	0.021
Operating time	226 [181–286]	218 [169–272]	0.48[b]	0.072
Tumor type				0.163
Benign	23/149 (16%)	33/149 (23%)	0.12[b]	
Malignant	116/149 (79%)	105/149 (72%)	0.19[b]	
Borderline	8/149 (5%)	7/149 (5%)	0.81[b]	
None	2/149 (1%)	4/149 (3%)	0.39[b]	
Indication for surgery*				0.003
Cervical cancer	10/149 (10%)	9/149 (9%)	0.85[b]	
Uterine (nonsarcoma)	20/149 (20%)	20/149 (19%)	0.94[b]	
Fallopian Tube	2/149 (2%)	5/149 (5%)	0.24[c]	
Ovary	60/149 (59%)	54/149 (54%)	0.49[b]	
Peritoneum	8/149 (8%)	10/149 (10%)	0.60[b]	
Uterine (sarcoma)	1/149 (1%)	1/149 (1%)	0.94[c]	
Other	2/149 (2%)	2/149 (2%)	1.00[c]	
Missing				
Epidural	1/149 (1%)	1/149 (1%)	1.00[c]	0.004
Previous surgery	78/149 (53%)	75/149 (50%)	0.68[b]	0.057
Celecoxib	138/149 (93%)	140/149 (94%)	0.64[b]	0.053
Pregabalin	119/149 (80%)	115/149 (77%)	0.52[b]	0.046
Tramadol	127/149 (86%)	127/149 (85%)	0.84[b]	0.002
IV acetaminophen	144/149 (97%)	143/149 (96%)	0.76[b]	0.035
Intraoperative transfusion	8/149 (5%)	9/149 (6%)	0.80[b]	0.029

Numbers are medians [interquartile ranges] or *n*/total *N* (%)

ASA = American Society of Anesthesiologists; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; SMD = standardized mean difference

*Only includes cancer diagnoses

[a]Mann–Whitney U test

[b]Chi square test

[c]Fisher's exact test

Table 3 Postoperative outcomes within 30 days after surgery

Variable	Opioid-sparing anesthesia $N = 149$	Opioid-based anesthesia $N = 149$	P value
Intraoperative opioid (MME [mg])	30 [25–55]	58 [38–70]	< 0.001
Postoperative opioid (MME [mg])	23 [0–94]	35 [13–95]	0.05[a]
PACU	2.5 [0–10]	5 [0–15]	0.005
Floor	15 [0–86.3]	27.5 [7.5–77.5]	0.10[a]
Length of stay	3 [2–4]	3 [2–4]	0.73[a]
Postoperative complications			
Hypoxia	3/149 (2%)	3/149 (2%)	1.00[b]
Atelectasis	1/149 (1%)	1/149 (1%)	1.00[b]
Hypotension	5/149 (3%)	1/149 (1%)	0.10[b]
Arrhythmia	0/149 (0%)	1/149 (1%)	0.32[b]
Tachycardia	6/149 (4%)	5/149 (3%)	0.76[b]
Acute kidney injury risk	7/149 (5%)	1/149 (1%)	0.03[b]
Acute kidney injury	10/149 (7%)	4/149 (3%)	0.10[c]
Acute kidney failure	0/149 (0%)	1/149 (1%)	0.32[b]
Urinary tract infection	7/149 (5%)	0/149 (0%)	0.01[b]
Urinary retention	6/149 (4%)	1/149 (1%)	0.06[b]
Constipation	5/149 (3%)	2/149 (1%)	0.23[b]
PONV	17/149 (11%)	11/149 (7%)	0.23[c]
Readmission	18/149 (12%)	16/149 (11%)	0.72[c]
Reoperation	3/149 (3%)	2/149 (2%)	0.33[b]

Numbers are medians [interquartile ranges] or *n*/total *N* (%)

MME = morphine milligram equivalents; PACU = postanesthesia care unit; PONV = postoperative nausea and vomiting

[a]Mann–Whitney U test

[b]Fisher's exact test

[c]Chi square test

gynecologic surgery compared to opioid-based anesthesia. Although opioid-sparing anesthesia reduced opioid administration during surgery and immediately after surgery in the PACU, there were no differences in total postoperative opioid consumption between cohorts. The level of constipation was 0.99–1.03 points higher in the opioid-sparing cohort than in the opioid-based cohort at POD 2 and POD 3. Additionally, patients receiving opioid-sparing anesthesia were more likely to develop postoperative AKI risk compared with those receiving opioid-based anesthesia.

Postoperative pain and opioid consumption delay hospital discharge and compromise patient functional recovery in the long term.[27] Hence, there is a global need to identify strategies that relieve pain and minimize opioid administration during hospitalization.[28] As a result, an appropriate anesthetic plan plays a fundamental role in the implementation of opioid-sparing modalities to enhance patient recovery and reduce ORADEs.[29] Both perioperative multimodal analgesia and regional anesthetic techniques have improved postoperative pain control and reduced perioperative opioid consumption.[30] More recently, the concept of multimodal intravenous anesthesia emerged as a technique using pharmacologic adjuvants to provide pain relief by blocking multiple nociceptive pathways, thereby achieving adequate pain control after surgery.[9,31] In our institution, opioid-sparing anesthesia is mainly composed of adjuvants that have shown postoperative analgesic properties, such as dexmedetomidine and ketamine, which have shown to provide prolonged analgesic properties (central α_2-adrenoceptor agonist and noncompetitive N-methyl-D-aspartate receptor antagonist), thereby explaining the reduction of opioid administration during surgery and in the PACU.[29] Although recent evidence supported the use of both agents as a safe and effective technique to relieve pain while reducing opioid consumption,[32,33] it is unknown whether this anesthetic technique affects PROs in either the short term or long term.[14] We observed less opioid consumption in the PACU among patients receiving

Table 4 Multiple comparisons of in-hospital patient-reported outcomes between opioid-sparing anesthesia and opioid-based anesthesia (reference group) in the matched cohort (units given in points of interference on a scale from 0 to 10)

Patient-reported outcome	POD 1			POD 2			POD 3		
	Coef.	95% CI	P value*	Coef.	95% CI	*P* value*	Coef.	95% CI	*P* value*
Interference with activities									
Walking	-0.33	-0.96 to 0.30	0.98	-0.28	-0.87 to 0.31	0.99	-0.25	-0.82 to 0.32	0.99
Relationship	-0.12	-0.63 to 0.38	0.99	-0.01	-0.49 to 0.46	0.99	-0.13	-0.59 to 0.33	0.99
General activity	-0.16	-0.89 to 0.56	0.99	-0.17	-0.78 to 0.44	0.99	-0.20	-0.82 to 0.41	0.99
Working	-0.16	-0.93 to 0.61	0.99	-0.05	-0.76 to 0.65	0.99	-0.31	-1.01 to 0.40	0.99
Mood	-0.01	-0.57 to 0.54	0.99	+0.08	-0.43 to 0.58	0.99	-0.02	-0.51 to 0.47	0.99
Enjoyment	-0.15	-0.75 to 0.46	0.99	-0.21	-0.83 to 0.41	0.99	-0.30	-0.92 to 0.33	0.99
Secondary outcomes									
Constipation	+0.83	0.25 to 1.41	0.08	**+1.03**	**0.44 to 1.63**	**0.02**	**+0.99**	**0.39 to 1.59**	**0.02**
Attention	-0.44	-0.84 to -0.06	0.39	-0.28	-0.65 to 0.09	0.89	-0.27	-0.63 to 0.09	0.93
Memory	+0.37	-0.11 to 0.86	0.88	+0.39	-0.06 to 0.85	0.78	+0.33	-0.12 to 0.77	0.93
Appetite	+0.15	-0.37 to 0.68	0.99	+0.24	-0.29 to 0.78	0.99	+0.22	-0.32 to 0.75	0.99
Pain	-0.15	-0.78 to 0.48	0.99	+0.07	-0.45 to 0.59	0.99	+0.09	-0.44 to 0.62	0.99
Nausea	-0.29	-0.74 to 0.16	0.96	-0.15	-0.58 to 0.28	0.99	-0.06	-0.48 to 0.37	0.99
Vomiting	-0.18	-0.47 to 0.11	0.96	+0.15	-0.41 to 0.12	0.99	-0.03	-0.29 to 0.23	0.99
Drowsiness	+0.18	-0.43 to 0.78	0.99	+0.26	-0.28 to 0.80	0.99	+0.19	-0.34 to 0.73	0.99
Bloating	+0.08	-0.52 to 0.69	0.99	+0.21	-0.37 to 0.80	0.99	+0.21	-0.35 to 0.77	0.99
Fatigue	+0.13	-0.49 to 0.76	0.99	+0.28	-0.32 to 0.88	0.99	+0.13	-0.46 to 0.71	0.99
Shortness of breath	+0.14	-0.27 to 0.56	0.99	+0.14	-0.24 to 0.52	0.99	+0.05	-0.34 to 0.43	0.99

Bold values are statistically significant ($P < 0.05$)

CI = confidence interval; Coef. = Coefficient; POD = postoperative day

*Holm–Bonferroni adjusted *P* values

opioid-sparing anesthesia, but this reduction was not considered to be clinically important and the differences were not significant for most of the PROs evaluated or for total postoperative opioid consumption. These findings elucidate the fact that reducing opioids with opioid-sparing anesthesia techniques does not necessarily affect PROs during hospital stay and after discharge. Some of the reasons that can explain the lack of difference in PROs in this study include the short action of dexmedetomidine and ketamine, the context of multimodal analgesia, standardization of opioid-prescribing practice, and procedure-specific analgesic combinations.[2] Interestingly, in the sensitivity analysis, we found that among patients with low compliance with ERAS (< 80%) opioid-sparing anesthesia reduced patient-reported nausea by −1.13 points, which may be due to the reduction of opioid consumption in the PACU and the greater number of nausea events in this subgroup, which allowed us to observe this effect.

Our study also highlights the limitations of opioid-sparing strategies.[2] We found that the levels of constipation were consistently higher at POD 2 and POD 3 in the opioid-sparing anesthesia cohort. We presume that this late-onset effect was secondary to unmeasured confounders (preoperative bowel function, postoperative bowel regimen). The difference in the level of constipation was between 1.03 and 0.99 points, which was not clinically important based on the clinical minimal important difference above the half of SD for that particular PRO according to the MDASI.[26]

Other postoperative adverse events that have been related to opioid-free anesthesia are hypoxemia and bradycardia. The Postoperative and Opioid-free Anesthesia (POFA) trial concluded that an opioid-free anesthetic regimen based on dexmedetomidine results in greater incidence of postoperative hypoxemic events.[12] Therefore, according to the current evidence from the POFA trial and our study, opioid-sparing anesthetic techniques may have potential adverse events. In our study, the rate of AKI was elevated in patients who received opioid-sparing anesthesia, which might be attributed to the tendency of anesthesiologists in our institution to use goal-directed fluid therapy defined as the use of an algorithmic-based decision to guide fluid

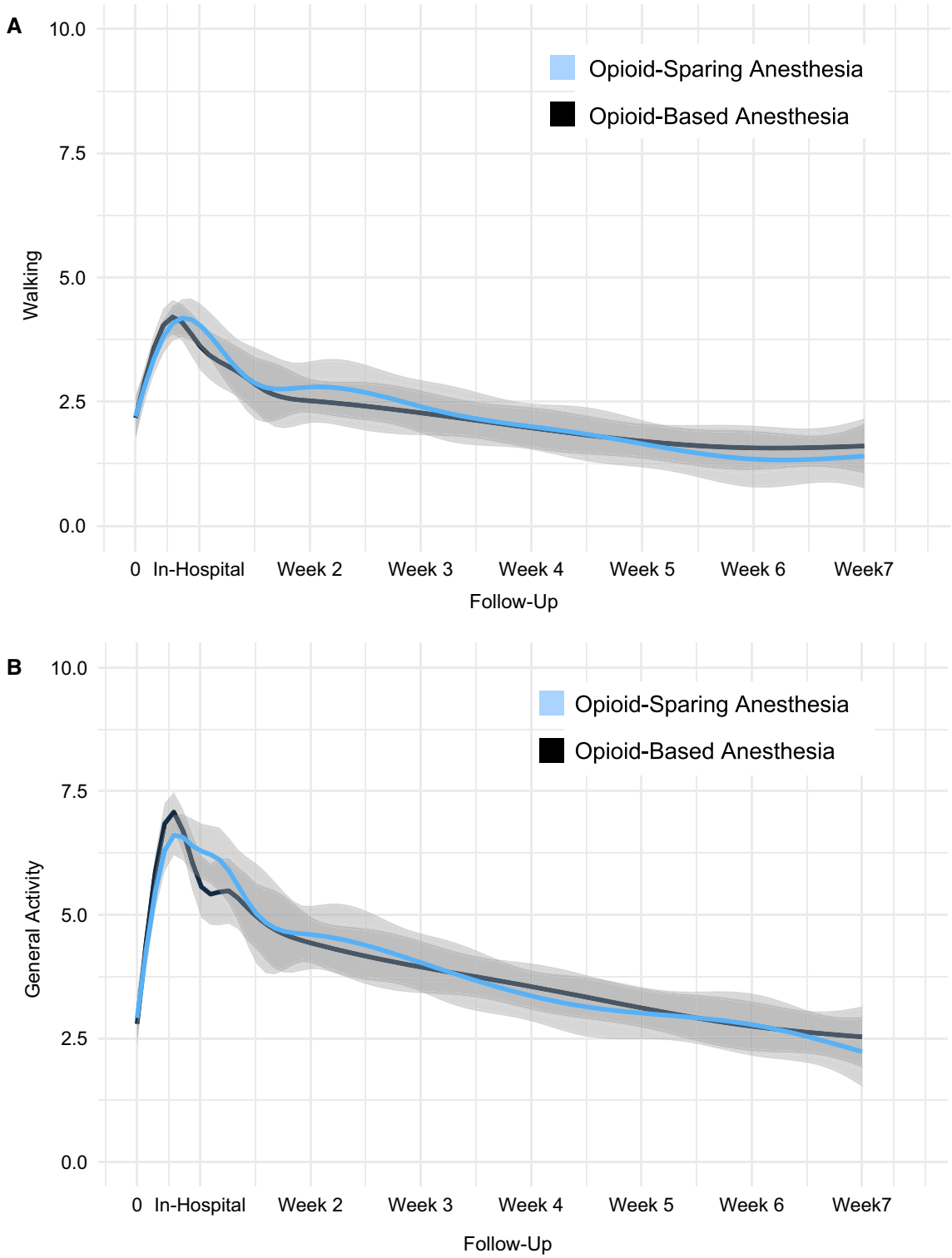

Fig. 2 Longitudinal comparison between opioid-sparing *vs* opioid-based anesthesia in the (*A*) interference with walking and (*B*) interference with general activity, from hospital admission through postoperative week 7

administration and maintain normovolemia, as shown in our previous study,[34] though there was no difference in the net balance between patients who receive multimodal anesthesia and those receiving standard anesthesia.[19,22] Another unmeasured factor that might influence higher rates of AKI in patients receiving opioid-sparing anesthesia is the preference for nonsteroidal anti-inflammatory drugs, which are frequently administered before and after surgery.

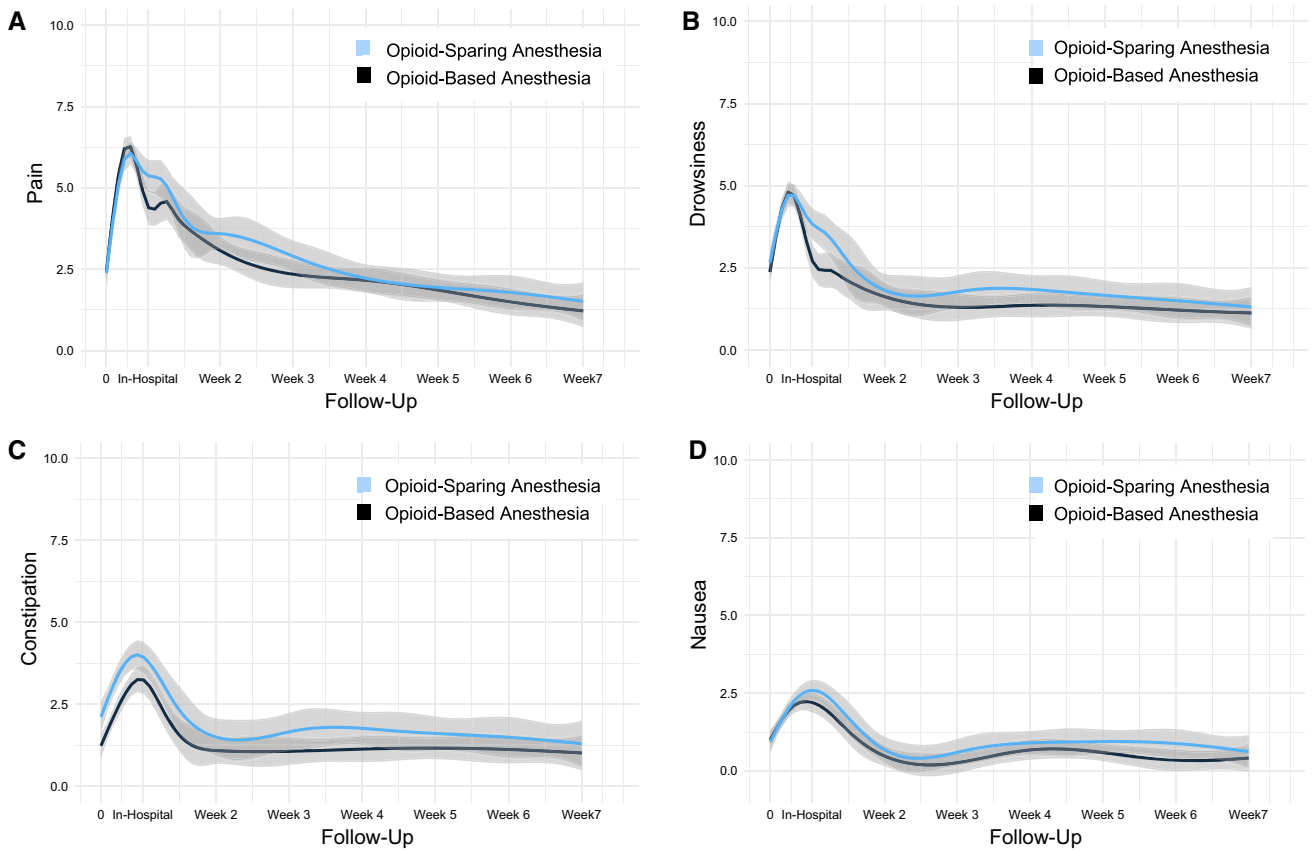

Fig. 3 Longitudinal comparison between opioid-sparing *vs* opioid-based anesthesia in secondary patient-reported outcomes (*A*—pain, *B*—drowsiness, *C*—constipation, *D*—nausea) from hospital admission to postoperative week 7

There were no significant differences in PROs between opioid-sparing anesthesia and opioid-based anesthesia. Several randomized controlled trials have shown the efficacy of opioid-free anesthesia in improving short-term pain and reducing ORADEs, but there is little evidence on PROs. Mulier *et al.* observed better quality of recovery (measured by the QoR-40) within the first 24 hr after laparoscopic bariatric surgery and lower pain scores in the PACU among patients receiving opioid-free anesthesia.[35] Similar results were reproduced in ambulatory gynecologic laparoscopy by Hakim *et al.*[36] In another study, Salem *et al.*[37] concluded that opioid-free anesthesia reduces postoperative nausea and vomiting and accelerates time to ambulation. On the contrary, Bakan *et al.*[38] refuted any benefit in terms of postoperative nausea or vomiting from opioid-free anesthesia and Devine *et al.*[39] found no differences in pain scores or postoperative opioid requirements after lung cancer resection in a case–control study comparing opioid-free anesthesia with standard anesthesia.

The current ERAS Society guidelines for gynecologic oncology recommend the use of short-acting anesthetics,[10] but there are still a broad number of multimodal analgesic options and the quality of the evidence is low.[6,9] Additionally, these guidelines support the intraoperative use of multiple analgesic modalities including regional anesthetic techniques and intravenous infusion of adjuvants such as ketamine, dexmedetomidine, and/or lidocaine. More research is needed to elucidate the optimal combination of multimodal techniques to set standards in the practice of anesthesia.

This study has a number of strengths which allow us to better understand the impact of opioid-sparing anesthetic techniques. First, it provided information about PROs and analyzed outcomes at long term. This information can be used by clinicians to guide intraoperative analgesic therapies and weigh risk–benefits of each anesthetic technique. Nevertheless, our analysis has several limitations that should be considered. First, there may be residual confounding bias in the propensity score model due to the lack of adjustment for other unmeasured factors such as frailty, psychiatric history, anxiety, intraoperative hemodynamic effects of dexmedetomidine (hypotension and bradycardia), anesthesiologist practice, and the use of preoperative medications, especially benzodiazepines. We could not perform adjustments for anesthesia providers

Table 5 Multilevel linear mixed-effects model for the longitudinal assessment of patient-reported outcomes after discharge (units given in points of interference on a scale from 0 to 10)

Patient-reported outcome	Coef.	95% CI	*P* value	Bonferroni *P* value
Interference with activities				
General activity	−0.01	-0.61 to 0.59	0.97	0.99
Walking	−0.03	-0.51 to 0.46	0.92	0.99
Mood	−0.08	-0.51 to 0.35	0.73	0.99
Working	−0.04	-0.69 to 0.61	0.91	0.99
Relationship	−0.13	-0.55 to 0.30	0.56	0.99
Enjoyment	−0.16	-0.67 to 0.35	0.53	0.99
Secondary outcomes				
Pain	+0.31	-0.17 to 0.79	0.21	0.97
Vomiting	+0.29	-0.64 to 0.07	0.12	0.87
Drowsiness	+0.41	-0.02 to 0.83	0.06	0.67
Attention	−0.02	-0.31 to 0.28	0.91	0.99
Memory	−0.01	-0.36 to 0.35	0.97	0.99
Fatigue	+0.45	-0.03 to 0.94	0.07	0.71
Appetite	+0.19	-0.25 to 0.63	0.41	0.99
Urinary urgency	+0.16	-0.12 to 0.45	0.27	0.98
Nausea	+0.15	-0.14 to 0.44	0.33	0.99
Constipation	+0.24	-0.20 to 0.68	0.29	0.98
Bloating	+0.13	-0.28 to 0.54	0.53	0.99
Shortness of breath	+0.11	-0.19 to 0.39	0.48	0.99

CI = confidence interval; Coef. = coefficient

because data collected before our institutional transition to an electronic medical record system in 2016 were missing. Furthermore, our analysis is at risk of selection bias because the patient population who consented to this study was selected based on other study protocols. Although the number of patients included in our matched cohort was higher compared with previous trials, we acknowledge that our findings should be interpreted with caution as they may be underpowered due to the reduction of the sample size after matching both groups. The statistical power of this study was 72.9% based on the final sample size of 498 patients. The effect size that we were powered to observe was a 33% reduction of interference with walking (from 5 to 3.3). Therefore, further large, randomized trials are needed to assess PROs in these settings to further elucidate any difference between opioid-sparing anesthesia *vs* opioid-based anesthesia. Another limitation of this study was the retrospective nature, which did not allow us to conclude causality. Given that this study is from a single center, the external validity of our results may be compromised because of practice variability in other institutions. There is also risk of selection bias due to the personal anesthetic choice by each anesthesiologist in our institution. There is lack of information, such as intraoperative hypotension rates to explain the association between opioid-sparing anesthesia and AKI risk. Additionally, we are unable to determine whether anesthesiologists tend to use less intraoperative opioids due to their intention of spare opioid administration or if it was a true effect from the combination of dexmedetomidine and ketamine infusions.

In summary, our multimodal opioid-sparing anesthetic regimen (dexmedetomidine and ketamine) is associated with lower opioid-based anesthesia and lower opioid administration at the PACU, and it did not result in any difference of PROs or total postoperative opioid consumption during hospitalization. Nevertheless, there was an increased rate risk of postoperative AKI among patients who received opioid-sparing anesthesia. Other anesthetic combinations, such as lidocaine, in conjunction with a patient-centered perioperative care approach should be investigated in terms of quality of recovery.

Author contributions *Andres Zorrilla-Vaca* designed the study, helped write the manuscript, performed statistical analysis, interpreted the results, and approved the final manuscript. *Larissa Meyer* and *Javier D. Lasala* designed the study, helped write the manuscript, interpreted the results, and approved the final manuscript. *Maria Iniesta-Donate* helped write the manuscript, collected data, interpreted the results, and approved the final manuscript. *Xin Shelley*

Wang, *Loretta A. Williams*, *Pedro T. Ramirez*, and *Gabriel E. Mena* helped write the manuscript, interpreted the results, and approved the final manuscript.

Disclosures Loretta A. Williams reports research funding from AstraZeneca, consulting for Glaxo-Smith-Kline, and stocks in Crispr and Bristol-Myers Squibb. Loretta A. Williams reports grants from AstraZeneca, Astellas, Bayer, Bristol Meyers Squibb, Genentech, Merck, and Eli Lily. Gabriel E. Mena reports a research/academic grant from PACIRA Pharmaceutical. The remaining authors report no conflicts of interest related to the subject matter of this manuscript.

Funding statement This work was supported in part by the MD Anderson Cancer Center Support Grant from the National Cancer Institute of the National Institutes of Health (NIH/NCI P30 CA016672) and the T32 training grant CA101642. Larissa Meyer was supported by a NIH-NCIK07-CA201013 grant.

Editorial responsibility This submission was handled by Dr. Stephan K. W. Schwarz, Editor-in-Chief, *Canadian Journal of Anesthesia/Journal canadien d'anesthésie.*

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