

Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis

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Editor's key points

- Bariatric surgery is commonly associated with postoperative nausea and vomiting (PONV).
- The authors compared PONV among bariatric surgery patients randomized to opioid-free total i.v. anaesthesia (TIVA) or volatile-opioid anaesthesia.
- The incidence and severity of PONV were significantly lower in the opioid-free TIVA group.

Background. Patients undergoing bariatric surgery are at high risk of postoperative nausea and vomiting (PONV). Despite triple PONV prophylaxis, up to 42.7% of patients require antiemetic rescue medication (AERM).

Methods. This prospective, randomized study was conducted from November 2011 to October 2012. In the Classic group ($n=59$), patients underwent general anaesthesia with volatile anaesthetics and opioids. In the Total i.v. anaesthesia (TIVA) group ($n=60$), patients underwent opioid-free TIVA with propofol, ketamine, and dexmedetomidine. The severity of PONV was assessed using a Likert scale (none, mild, moderate, and severe).

Results. Patients in both groups had similar clinical characteristics, surgical procedure, and PONV risk scores and required similar amounts of postoperative opioid. In the Classic group, 22 patients (37.3%) reported PONV compared with 12 patients (20.0%) in the TIVA group [$P=0.04$; risk 1.27 (1.01–1.61)]. The absolute risk reduction was 17.3% (number-needed-to-treat=6). The severity of nausea was statistically different in both groups ($P=0.02$). The severity of PONV was significantly worse in the Classic group. There was no difference either in the number of patients requiring AERM in the postoperative period or in the number of AERM doses required.

Conclusions. This prospective randomized study demonstrates that opioid-free TIVA is associated with a large reduction in relative risk of PONV compared with balanced anaesthesia.

Clinical trial registration. NCT 01449708 (ClinicalTrials.gov).

Keywords: anaesthetics i.v., propofol; analgesic techniques; obesity; PONV; vomiting, nausea, anaesthetic factors

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Patients after bariatric surgery are at high risk of postoperative nausea and vomiting (PONV). Despite triple PONV prophylaxis with dexamethasone, ondansetron and the scopolamine patch (TDS), up to 42.7% of patients required antiemetic rescue medication (AERM).¹ In this study, the number of patients undergoing laparoscopic Roux-en-Y gastric bypass (LRYGB) surgery requiring AERM was reduced by 14.6% after replacing postoperative opioids with a multimodal approach. However, 32.1% of patients required AERM despite triple PONV prophylaxis and the use of multimodal analgesia.¹

Total i.v. anaesthesia (TIVA) with propofol for maintenance of general anaesthesia reduces the risk of PONV² and intraoperative opioid medication seems to increase the risk of PONV.³ In a previous study, dexmedetomidine was used effectively to replace intraoperative fentanyl in open gastric bypass surgery.⁴

The hypothesis of this study was that opioid-free TIVA (TIVA group) compared with inhalation anaesthesia with opioids (Classic group) is able to reduce PONV in patients after laparoscopic bariatric surgery treated with triple PONV prophylaxis.

Methods

Trial design

This prospective, randomized parallel-group single-centre study was conducted at Flagler Hospital, St Augustine, FL, USA. The current study complies with the Declaration of Helsinki, was approved by the local Institutional Review Board (Flagler Life Institute, St Augustine, FL, USA, #00006886) and was registered with ClinicalTrials.gov (NCT 01449708). All the patients gave written consent.

Participants

All the patients older than 18 yr undergoing elective bariatric surgery [gastric band (GB), LRYGB, revision of a LRYGB, removal of GB then LRYGB (Conversion), and sleeve gastrectomy (SG)] at Flagler Hospital from November 2011 to October 2012 were screened. Patients taking high doses of opioids before operation for chronic pain or patients with

allergies to any study medication were excluded. Intraoperative administration of opioids or utilization of volatile anaesthetics in the TIVA group was considered a protocol violation and patients were excluded from the analysis. Patients that failed to receive one component of triple PONV prophylaxis were included in the analysis.

After enrolment into the study, patients were randomized to the Classic group or TIVA group. The randomization was computer-generated using www.random.org.

Power analysis

The incidence of PONV is 42.7% in patients after bariatric surgery at Flagler Hospital.¹ It was assumed that the avoidance of intraoperative opioids and of volatile anaesthetics could reduce the absolute risk by 25%. With a level of significance=0.05 and a power=0.8 each group required 58 patients.

Blinding

Patients were blinded to their group assignment. Neither the anaesthesia team nor the postoperative anaesthesia care unit (PACU) nurses were blinded. Nurses on the ward were blinded to the group assignment. On the first postoperative day (POD), after answering study questions, the group assignment was revealed to the patient. The investigator assessing the degree of PONV on the first POD was blinded to the treatment.

Anaesthetic management

All the patients undergoing elective bariatric surgery received 2–4 mg i.v. midazolam before the operation.

Induction of general anaesthesia

Routine monitoring was applied in the operating theatre (OT). Patients were preoxygenated until end-tidal oxygen fraction was >90% or no further increase could be detected. Anaesthesia was induced with propofol (1–2.5 mg kg⁻¹ i.v.) and succinylcholine (1–1.5 mg kg⁻¹ i.v.) or rocuronium (0.5–1.0 mg kg⁻¹ i.v.).

After induction and intubation, muscle relaxation was maintained with boluses of rocuronium (10–20 mg) or vecuronium (1–2 mg) to provide optimal surgical conditions. Patients were ventilated with a mixture of oxygen and air. At the end of surgery, muscle relaxation was reversed with neostigmine (up to 5 mg) and glycopyrrolate (0.2–0.8 mg).

Medication was administered based on actual total body weight when indicated. All the patients received i.v. acetaminophen (1000 mg) ~20 min after induction and i.v. ketorolac (30 mg) ~20 min before emergence.

Classic group

In the OT, fentanyl (0.5–1 µg kg⁻¹ i.v.) was administered before induction of general anaesthesia (GA). GA was maintained with inhalation anaesthetics (sevoflurane or desflurane) at a minimum alveolar concentration of 0.7–1.3 and intermittent boluses of fentanyl, morphine, or hydromorphone at the anaesthesia provider's discretion. The BIS[®] monitor was not routinely used in the Classic group.

TIVA group

In the OT a loading dose of dexmedetomidine (0.5 µg kg⁻¹ i.v. over 10 min) was initiated. GA was maintained with an i.v. infusion of dexmedetomidine (0.1–0.3 µg kg⁻¹ h⁻¹) and an i.v. infusion of propofol (75–150 µg kg⁻¹ min⁻¹) titrated to a BIS[®] between 40 and 60. Before incision a single dose of ketamine (0.5 mg kg⁻¹ i.v.) was given.

Prevention and management of PONV

On the morning of surgery a TDS was applied. Dexamethasone (4–10 mg i.v.) was administered ~10 min after induction of GA and ondansetron (4 mg i.v.) ~20 min before the end of the operation. If patients complained of PONV in the PACU droperidol (0.625 mg i.v.) or promethazine (6.25 mg i.v.) was administered. Patients complaining of PONV after discharge from the PACU received ondansetron (4 mg i.v.) or promethazine (6.25–12.5 mg i.v.).

On the morning of the first POD, ondansetron was administered routinely to prevent nausea from the contrast agent used for an upper gastrointestinal (GI) series in patients after laparoscopic gastric bypass or a revision of a gastric bypass. This was not counted as an AERM. Patients after laparoscopic sleeve gastrectomy do not routinely get an upper GI series.

Detailed postoperative multimodal pain management and pain assessment is described in detail elsewhere.¹

Postoperative multimodal pain management

Postoperative pain was treated with i.v. acetaminophen (1000 mg) and i.v. ketorolac (30 mg) every 6 h for the first 24 h. Postoperative pain was measured on an 11-point numeric point scale (NPS). Patients experiencing postoperative breakthrough pain received either oral oxycodone or i.v. hydromorphone depending on the severity of pain. The oral oxycodone dose was converted into hydromorphone for the purpose of analysis (20 mg oral oxycodone=1.5 mg i.v. hydromorphone; 10 mg i.v. morphine=1.5 mg i.v. hydromorphone).⁵

Pain assessment

The level of pain was assessed on an 11-point NPS. Patients were asked to determine their own 'acceptable' pain score. At night sleeping patients were not woken to assess the VAS score.

Data collection

Clinical characteristics (height and weight), PONV risk factors, surgical procedure, type of anaesthesia, surgical times, opioid consumption, pain intensity, and the number of antiemetic doses were assessed.

Assessment/interview

Patients were interviewed in the morning on the first POD. Patients were asked by one of the investigators to rate the worst episode of PONV on a four-point verbal rating scale (VRS) (none, mild, moderate, or severe). Patients were also asked whether they experienced retching or vomiting. After

the interview, the patients were informed about the group assignment.

Statistical analysis

The initial data were entered in an Excel® spreadsheet and later transferred to an R® data set for analysis. The categorical data were analysed with the χ^2 test for independence or the Fisher exact test. The quantitative data were analysed using the unpaired Student *t*-test for significance. If the data were not normally distributed as assessed by the Shapiro–Wilk test, the Wilcoxon rank-sum test was used. Ordinal data were analysed using the Wilcoxon rank-sum test. Highly skewed quantitative data were presented as median with inter-quartile range (IQR) (doses of neostigmine, succinylcholine, and glycopyrrolate).

Results

Study protocol

A total of 160 patients underwent bariatric procedures in the study period. Seven patients did not qualify for the study:

three patients taking high doses of opioids before operation, three patients with allergies to one or more study medications, and one patient with chronic nausea and vomiting (Fig. 1).

Clinical characteristics were comparable in the two groups (see Table 1). Anaesthesia was provided in an anaesthesia care team [Anaesthesiologist/Certified Registered Nurse Anaesthetist (CRNA)] by 5 anaesthesiologists and 11 CRNAs.

Clinical characteristics

In the Classic group, 6 patients (10.2%) did not receive all components of triple PONV prophylaxis (5 patients did not receive dexamethasone and 1 patient did not receive ondansetron). In the TIVA group, 9 patients (15.0%) did not receive triple PONV prophylaxis (6 patients did not receive dexamethasone and 3 patients did not receive ondansetron). There was no significant difference ($P=0.60$) and these patients were included in the analysis. All the patients received at least two different medications as PONV prophylaxis (Table 1).

There was no significant difference in the risk score for PONV ($P=0.38$) (see Table 2). All the patients were required to quit

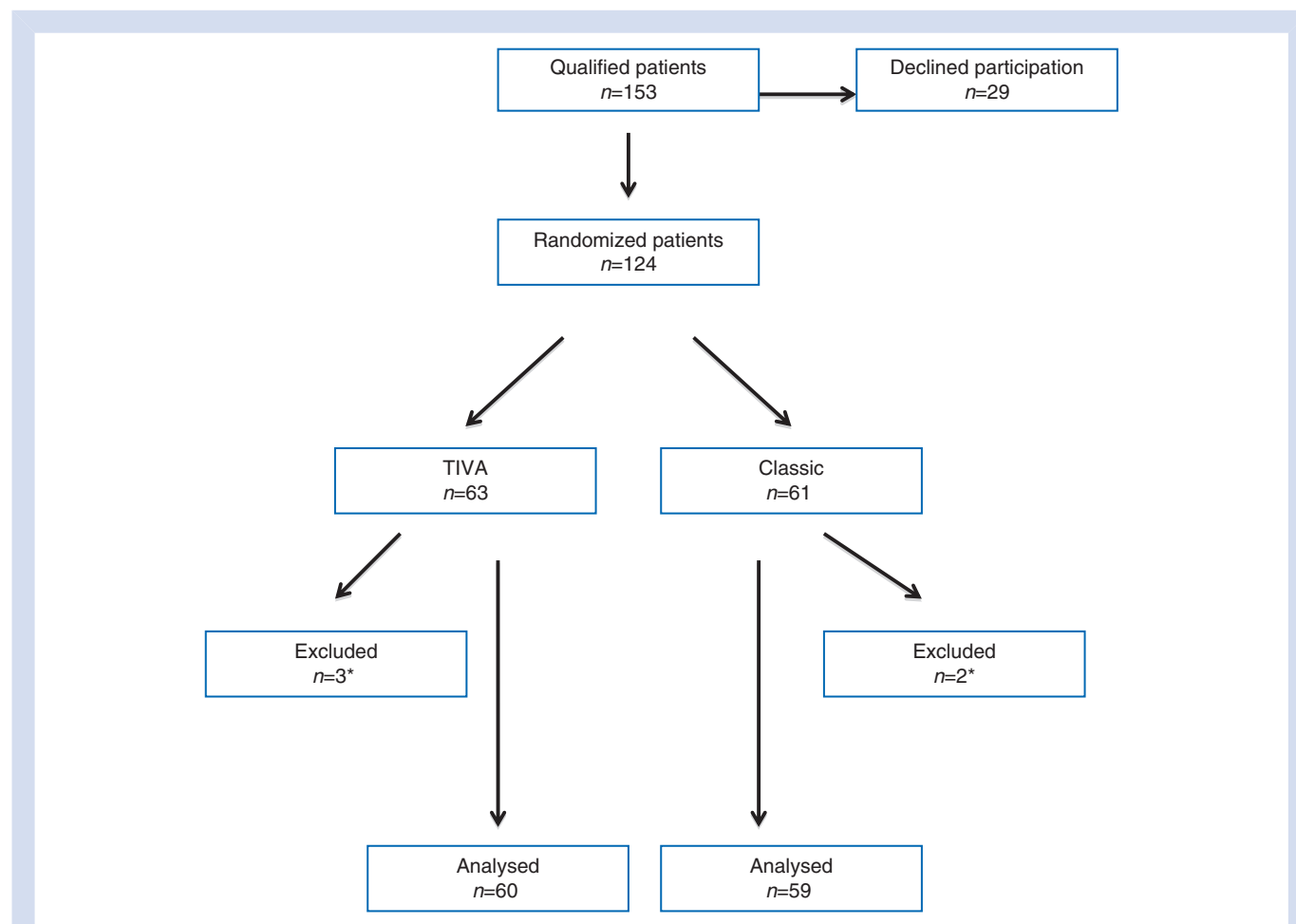


Fig 1 Study protocol. *Reasons for exclusion from the analysis: TIVA group: 1—protocol violation, received narcotics. 2—possible anastomotic instability, intraoperative J-tube placement. 3—converted to open gastric bypass surgery, postoperative mechanical ventilation. Classic-group: 1—hypercarbic respiratory failure with somnolence and ICU admission. 2—postoperative intra-abdominal haematoma requiring re-exploration on POD 1.

Table 1 Clinical characteristics. sd, standard deviation; f, female; m, male; BMI, body mass index. Times are shown in hours:minutes. *Wilcoxon rank-sum test; †Fisher's exact test; ‡Student's *t*-test. LRYGB, laparoscopic Roux-en-Y gastric bypass; SG, sleeve gastrectomy; GB, gastric band; Conversion, removal of GB followed by LRYGB

	Classic group (n=59)	TIVA group (n=60)	P-value
Age (sd)	50.4 (12.4)	50.5 (13.7)	0.96*
Gender (f/m)	43/16	39/21	0.47†
BMI (sd)	45.32 (6.97)	44.15 (7.46)	0.38*
Anaesthesia time (sd)	2:55 (0:57)	3:15 (1:13)	0.15‡
Surgical time (sd)	1:58 (0:50)	2:11 (1:09)	0.23‡
LRYGB	33 (55.9%)	39 (65.0%)	
SG	16 (27.1%)	13 (21.7%)	
Revision LRYGB	7 (11.9%)	6 (10.0%)	
GB	1 (1.7%)	0 (0%)	
Conversion	2 (3.4%)	2 (3.3%)	0.88†

Table 2 PONV risk score. PONV, postoperative nausea and vomiting. PONV risk score:⁶ 0–4 for female gender, non-smoker, history of PONV, and postoperative opioid use. Each point of the PONV risk score indicates that the patient has a 20% RR increase of developing PONV. * Wilcoxon rank-sum test

PONV risk score	Classic group (n=59)	TIVA group (n=60)	P-value*
1	0 (0%)	1 (1.7%)	
2	13 (22.1%)	20 (33.3%)	
3	35 (59.3%)	26 (43.3%)	
4	11 (18.6%)	13 (21.7%)	0.38

smoking before operation and only one patient admitted to smoking. After bariatric surgery, the use of postoperative opioids is anticipated. Consequently, there were no patients with a risk score of 0 and only one patient with a risk score of 1.⁶

PONV risk score

There was no significant difference in the surgical procedures performed ($P=0.88$) or perioperative times in either group (see Tables 1 and 2). PONV differed between surgical procedures ($P=0.001$). The incidence of PONV by surgical procedure was: SG—58.6%, LRYGB—19.4%, GB—0%, revision LRYGB—23.1%, and Conversion—0%. For the purposes of statistical analysis, surgical procedures involving a LRYGB were combined into the ReY Group (LRYGB, revision LRYGB, and Conversion). This leaves three groups (ReY, GB, and SG). PONV was different between the three groups ($P=0.009$). Comparing all the three groups, applying the Bonferroni correction ($\alpha/n=0.016$), PONV was more common in SG compared with the ReY group ($P=0.006$, OR 3.04; CI 1.28–7.29). The remaining comparisons were not significant.

Average hydromorphone doses were equivalent in the two groups in the postoperative period, 2.29 mg (± 1.52 mg) and 2.08 mg (± 1.17 mg), respectively ($P=0.40$). Median neostigmine and glycopyrrolate doses were higher in the TIVA group [5 mg (IQR 1) vs 4 mg (IQR 1.25)] ($P=0.005$) and [0.6 mg (IQR 0.4) vs 0.8 mg; (IQR 0.275)] ($P=0.04$), respectively.

There was no difference in the time from the end of the operation to PACU arrival time 16 min (± 13) vs 15 min (± 9) ($P=0.50$) and no difference in the time it took patients to meet the discharge criteria from PACU 44 min (± 23) vs 44 min (± 19) ($P=0.92$) in the Classic group vs the TIVA group. The acceptable pain scores ($P=0.53$) and pain scores on arrival on the ward ($P=0.66$) were not different. The median NPS on arrival to the ward was four for the Classic and four for the TIVA group. The 11-point NPS scores were taken at similar times of the day but at different times in relation to the end of surgery (except after PACU discharge and on arrival on the ward) and the patient's recovery. Therefore, we did not compare the remaining pain scores.

In the Classic group, 28 patients reported unacceptable pain scores at one time or more often in the first 24 h. In the TIVA group, 24 patients reported unacceptable pain scores at one point in the first 24 h ($P=0.24$).

Twenty-two patients (37.3%) reported PONV in the Classic group and 12 patients (20%) in the TIVA group (see Table 3). This is a significant reduction in PONV ($P=0.04$), with a RR reduction of 46.4%. The RR is 1.27 (1.01, 1.61). The number of patients requiring AERM was not different in the Classic group compared with the TIVA group. Patients required 48 doses of AERM in the Classic group and 26 doses of AERM in the TIVA group ($P=0.07$).

Patients requiring AERM and reporting PONV

The absolute risk reduction is 17.3% [$RR_{\text{Classic group}} - RR_{\text{TIVA}}$ (37.3–20.0%); number-needed-to-treat (NNT)=6 (5.78)]. There were two adverse events in the TIVA group. One patient developed a second degree AV block and one patient developed hypotension in PACU. No patient showed signs of a dysphoric reaction to ketamine. There was no difference in the number of patients requiring treatment for intraoperative bradycardia ($P=0.10$) (Table 3).

Comparison of PONV severity

The severity of nausea was different in both groups ($P=0.02$). In the Classic group more patients experienced retching than in the TIVA group. All the patients that reported retching rated the level of nausea as severe. Of the seven patients in the Classic group complaining of retching, five patients reported vomiting (Table 4).

Discussion

This prospective randomized study demonstrates that opioid-free TIVA was able to reduce the absolute risk of developing PONV by 17.3% (NNT=6) and the severity of PONV compared with GA using volatile anaesthetics and opioids in patients

Table 3 Patients requiring AERM and reporting PONV. CI, confidence interval; PONV_t, total number of patients reporting postoperative nausea and vomiting; AE_{PACU}, number of patients requiring AERM in PACU; AE_{post}, number of patients requiring AERM in the postoperative period, excluding PACU; AE_{total}, number of patients requiring AERM in the postoperative period. *Fisher's exact test

	Classic group (n=59)	TIVA group (n=60)	P-value*	RR (95% CI)
AE _{PACU} , n (%)	18 (30.5%)	13 (21.7%)	0.30	1.13 (0.91, 1.40)
AE _{post} , n (%)	16 (27.1%)	9 (15.0%)	0.12	1.17 (0.97, 1.41)
AE _{total} , n (%)	26 (44.1%)	17 (28.3%)	0.09	1.28 (0.97, 1.69)
PONV _t , n (%)	22 (37.3%)	12 (20.0%)	0.04	1.27 (1.01, 1.61)

Table 4 Comparison of PONV severity. CI, confidence interval; n/a, not applicable. *Wilcoxon rank-sum test; †Fisher's exact test

PONV severity	Classic group (n=59)	TIVA group (n=60)	P-value	RR (95% CI)
None	37 (62.7%)	48 (80.0%)		
Mild	13 (22.0%)	9 (15.0%)		
Moderate	2 (3.4%)	3 (5.0%)		
Severe	7 (11.9%)	0 (0%)	0.02*	n/a
Retching	7 (11.9%)	0 (0%)	0.006†	1.13 (1.02, 1.25)
Vomiting	5 (8.5%)	0 (0%)	0.02†	1.09 (1.00, 1.19)

undergoing bariatric operations. Patients in both groups had a comparable preoperative risk of developing PONV.

Volatile anaesthetics are known to increase the risk of developing PONV.⁷ The avoidance of volatile anaesthetics and higher doses of intraoperative opioids seem to reduce the risk of PONV.^{2,3} It is unclear in the literature whether the omission of intraoperative opioids in combination with TIVA can further reduce PONV in patients treated with triple PONV prophylaxis.

In the present study, the avoidance of both volatile anaesthetics and intraoperative opioids led to a high RR reduction in PONV (46.4%). TIVA has been reported to reduce the RR of PONV by 19%.² The reduction in our study group may have been related to the avoidance of intraoperative opioids. Though the comparison of those two RRs has to be interpreted with caution because of the different patient populations observed. Further confounding factors could have been the administration of dexmedetomidine and ketamine in the TIVA group. It is unclear whether either drug has an antiemetic effect beyond the degree of opioid reduction and ketamine may even possess emetogenic properties.^{8,9}

In a retrospective data analysis, the incidence of patients requiring AERM was lower.¹ Several factors could have influenced these differences. In the previous study, only patients after LRYGB were enrolled. In the present study, 60.5% of patients underwent LRYGB. There was no significant difference in the surgical procedures between the two groups in the present study. Patients after SG seem to have higher odds of developing PONV compared with LRYGB. Further healthcare providers in PACU and on the ward were aware that a study examining

the effects of different anaesthetic techniques on PONV was ongoing. This fact may have raised awareness among health care providers.

The study was not designed to determine a reduction in AERM. But the reduction in PONV did not lead to a difference in patients requiring AERM in the postoperative period or a significant reduction in AERM between the Classic group and the TIVA group.

A limitation of the current study is that PONV was assessed only at one time point. This may be considered a cumulative subjective incidence of PONV that may not reflect the 'true' incidence over time. Patients fear PONV as a postoperative complication.¹⁰ Therefore, the subjective experience and recollection of an adverse event (PONV) could influence the perception of the overall hospital experience.

The Centers for Medicare and Medicaid Services along with the Agency for Healthcare Research and Quality developed a nationwide hospital consumer assessment survey. This is a standardized survey instrument for measuring patients' perspectives on hospital care.¹¹ These data allow patients to objectively compare hospitals in a meaningful manner. A patient's perception or recollection of PONV may, based on this tool, be more important than the actual administration of AERM or 'true' incidence of PONV.

To quantify symptoms of PONV a visual analogue scale (VAS) or a VRS can be used although neither scale is validated in the assessment of PONV.^{12,13} We found that a VRS is an intuitive scale and easy to understand for patients.

The PONV intensity scale is a valid measure of clinically important PONV in the perioperative period and its use could have increased the validity of the presented data, though only one-fifth of the patients with PONV demonstrate clinically important PONV.^{13,14}

Another limitation of the current study is that only data from patients who completed the study and received the allocated intervention (per protocol analysis) were included. Intention-to-treat (ITT) analysis is preferred for superiority trials. ITT analysis aims to include all participants randomized into a trial irrespective of what happened subsequently and would have given a more conservative estimate of the results reducing the chance of a type-1 error.¹⁵

Further, blinding of all the providers involved would have increased the validity of the data, but this was not possible intraoperatively because of the differences of the interventions and drug applications.

Conclusion

Opioid-free TIVA was able to reduce PONV and the severity of PONV compared with inhalation anaesthesia combined with opioids in patients undergoing bariatric operations treated with triple PONV prophylaxis.

Authors' contributions

P.Z.-G. helped design the study, conduct the study, analyse the data, and write the manuscript. A.A.G. helped conduct the study, analyse the data, and write the manuscript. J.K. has seen the original study data, helped conduct the study, and approved the final manuscript. R.T.M. helped design the study, conduct the study, and write the manuscript.

Declaration of interest

P.Z.-G. received honoraria from Cadence[®] and Baxter[®]. P.Z.-G. is shareholder of Cadence[®] and J&J[®]. Cadence[®] produces and distributes i.v. acetaminophen (Ofirmev[®]). Baxter[®] produces and distributes the Transderm[®] scopolamine patch. Both drugs were used in both groups and were not part of the investigation. No funding was provided by any of these companies and the medication was purchased through our hospital pharmacy. A.A.G. is a shareholder of J&J[®]. J.K. declared no conflict of interest. R.T.M. received honoraria from Ethicon[®] Endosurgery, Transenterix[®] and Synovis[®] Surgical.

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