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의학 박사 학위논문

**Effect of dexmedetomidine
compared to remifentanyl during
bariatric surgery on postoperative
nausea and vomiting:
A retrospective study**

비만대사수술에서 텍스메데토미딘과
레미펜타닐이 수술 후 오심 및 구토에 미치는
영향 비교: 후향적 연구

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의학과 마취통증의학

남 선 우

A thesis of the degree of Doctor of Medical science

**비만대사수술에서
덱스메데토미딘과 레미펜타닐이
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**Effect of dexmedetomidine compared to
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Seoul National University College of Medicine

Department of Anesthesiology and Pain Medicine

Sun Woo Nam

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지도교수 오 아 영

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의학과 마취통증의학 전공

남 선 우

남선우의 의학 박사 학위논문을 인준함

2023 년 1 월

위 원 장 황 정 원 (인)

부 위 원 장 오 아 영 (인)

위 원 윤 유 석 (인)

위 원 공 현 식 (인)

위 원 이 예 지 (인)

Abstract

Purpose: Postoperative nausea and vomiting (PONV) occurs frequently after bariatric surgery and is a major cause of adverse outcomes. This retrospective study investigated whether opioid-restricted total intravenous anesthesia using dexmedetomidine as a substitute for remifentanyl can reduce PONV in bariatric surgery.

Materials and Methods: The electronic medical records of adult patients who underwent laparoscopic bariatric surgery between January and December 2019 were reviewed. The patients were divided into two groups according to the agents used for anesthesia: Group D, propofol and dexmedetomidine; Group R, propofol and remifentanyl.

Results: A total of 134 patients were included in the analyses. The frequency of postoperative nausea was significantly lower in Group D than Group R until 2 h after discharge from the post-anesthesia care unit (PACU) ($P = 0.005$ in the PACU, $P = 0.010$ at 2 h after PACU discharge), but failed to significantly reduce the overall high incidence rates of 60.5% and 65.5%, respectively ($P = 0.592$). Postoperative pain score was significantly lower in Group D until 6 h after PACU discharge. The rates of rescue antiemetic and analgesic agent administration in the PACU were significantly lower in Group

D than Group R.

Conclusion: Opioid-restricted total intravenous anesthesia using dexmedetomidine reduces postoperative nausea, pain score, antiemetic and analgesic requirements in the immediate postoperative period after bariatric surgery.

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Keywords: bariatric surgery, dexmedetomidine, postoperative nausea and vomiting

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Introduction

In the Asian population, obesity-related cardiovascular mortality and morbidity are more frequent, and occur at a lower body mass index (BMI), compared to the non-Asian populations. Therefore, surgical treatment of obesity is increasingly being incorporated into clinical guidelines and public health policy in many Asian countries.[1] In the Republic of Korea, bariatric and metabolic surgeries have been covered by the national health insurance system since January 2019, which led to an increase in the number of bariatric surgeries from 139 to 2,529 per year between 2003 and 2019. A recent report from Korea showed significantly higher cost-effectiveness of bariatric and metabolic surgeries compared to non-surgical treatment of obesity.[2] With the increasing demand for and accessibility of bariatric surgery, clinical management of obese patients has become a major area of focus.

The incidence of postoperative nausea and vomiting (PONV) is higher after bariatric surgery than after other surgeries, including non-bariatric gastric surgery; thus, it is a major factor associated with adverse outcomes.[3, 4] For example, PONV is the most common cause of readmission after bariatric surgery, increases medical costs, delays recovery and dietary progression, and can cause a number of complications, including dehydration, malnutrition, wound complications, and even anastomosis rupture.[5, 6]

Opioid reduction using various non-opioid adjuncts, including dexmedetomidine, is a commonly recommended method of PONV prophylaxis, along with total intravenous anesthesia (TIVA).[7] Dexmedetomidine, an alpha-2 adrenergic agonist, is a non-narcotic agent that has anesthetic and analgesic properties with a low rate of respiratory depression. As an advanced form of opioid reduction, it has recently been highlighted that opioid-restricted anesthetic regimens using dexmedetomidine reduce PONV and provide better postoperative pain control.[8, 9] The use of dexmedetomidine during bariatric surgery is associated with reduced intraoperative volatile anesthetic requirement, perioperative opioid use, and postoperative pain scores. However, studies have shown conflicting results regarding the effects on PONV and recovery time.[10–13]

This retrospective study investigated whether an opioid-restricted total intravenous anesthetic regimen using dexmedetomidine as a substitute for remifentanyl can reduce PONV in bariatric surgery.

Materials and methods

Study design

The Institutional Review Board of Seoul National University Bundang Hospital approved this retrospective, observational single-center study and waived the requirement for written informed consent because of the retrospective nature of the study.

The electronic medical records of patients who underwent elective laparoscopic bariatric surgery between January 2019 and December 2019 were reviewed. Inclusion criteria were patients aged 19–75 years who received propofol-based total intravenous anesthesia, including either dexmedetomidine or remifentanyl. Exclusion criteria were patients who received inhalation anesthetics during surgery, who did not use patient-controlled analgesia (PCA) devices after surgery, who were transferred to the intensive care unit (ICU) due to problems during surgery or recovery, and who underwent reoperation due to surgical complications during the hospital stay after surgery.

Anesthetic protocol

The patients were divided into two groups according to the agents used for anesthesia: Group D, propofol and dexmedetomidine; Group R, propofol and

remifentanyl. In Group D, anesthesia was induced with 1–2 mg/kg propofol and dexmedetomidine loading at a dose of 0.5 µg/kg for 5–10 min. To alleviate hemodynamic changes caused by endotracheal intubation, a single dose of 0–1000 µg alfentanil was administered. Anesthesia was maintained with continuous infusion of propofol (6–12 mg/kg/h) and continuous infusion of dexmedetomidine (0.1–0.6 µg/kg/h), without any additional opioids. In Group R, anesthesia induction and maintenance were achieved by continuous infusion of propofol (6–12 mg/kg/h) and target-controlled infusion (TCI; Minto model) of remifentanyl.

In both groups, 0.6–1.2 mg/kg rocuronium was administered for endotracheal intubation, and 50 mg/kg of magnesium sulfate was loaded over 10 min. After completion of magnesium sulfate loading, it was infused continuously at a rate of 15 mg/kg/h. Dexamethasone (5 mg) and ketorolac (30 mg) were given after the induction of anesthesia as components of multimodal analgesia. Local anesthetic was not infiltrated into the incision site. At the end of surgery, sugammadex or a combination of neostigmine and glycopyrrolate was administered based on the results of train-of-four (TOF) monitoring. Patient-controlled analgesia (PCA) was composed of a mixture of fentanyl (1500–2000 µg) and normal saline in a total volume of 100 mL. Ramosetron (0.3 mg) was given when the PCA device was connected.

Postoperative protocol

Patients recovered their oral diet starting with sips of water at postoperative day (POD) 1, a soft fluid diet (SFD) at POD 2, and were discharged on POD 3 if there were no adverse events. From the day of surgery, 40 mg pantoprazole was administered once a day parenterally or orally depending on the patient's diet status. A dose of 0.075 mg palonosetron was administered parenterally on POD 1. After the patients started SFD, tramadol (37.5 mg)/acetaminophen (325 mg) and Beszyme (a mixture of 30 mg bromelain, 40 mg dimethicone, and 400 mg pancreatin) were administered orally three times a day.

Data acquisition

Nausea, vomiting, postoperative pain score (expressed on an 11-point numerical rating scale [NRS]), administration of rescue antiemetic, and pain medication were investigated in the post-anesthesia care unit (PACU) and at 2 h, 2–6 h, 6–24 h, and 24–48 h after PACU discharge.

Statistical analysis

The primary outcome was the incidence of nausea in the postoperative period. The secondary outcomes were incidence of vomiting, rescue antiemetic administration, postoperative pain score, and rescue pain medication administration. The groups were compared using Student's t test or the Mann–

Whitney U test for continuous variables and χ^2 test or Fisher's exact test for categorical variables, with SPSS 25.0 software for Windows (SPSS Inc., Chicago, IL, USA). In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

A total of 140 patients who underwent laparoscopic bariatric surgery under propofol-based total intravenous anesthesia during the target period were identified. Four patients were excluded from the analysis because they were transferred to the ICU postoperatively. One patient who underwent bleeding control surgery in the immediate postoperative period and one patient who refused to use the PCA device were also excluded. Therefore, the final analysis was performed in 134 patients, consisting of 76 patients in Group D and 58 patients in Group R. No patients were given both dexmedetomidine and remifentanyl (Figure 1).

There were no significant differences in patient characteristics between the two groups (Table 1). Of the risk factors included in the simplified Apfel score, previous history of PONV or motion sickness could not be identified in the records of most patients, but one patient in Group D mentioned a history of PONV in the preanesthetic evaluation.

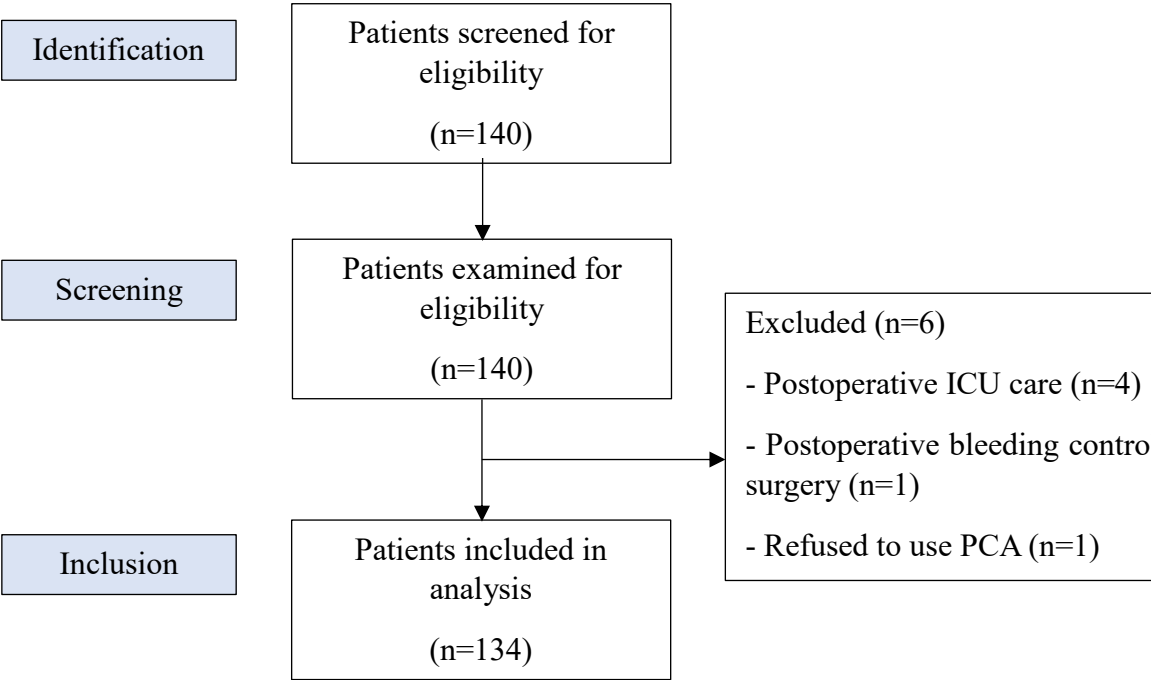
Table 2 shows the surgery and recovery characteristics of the two groups. The type of bariatric surgery performed at our institution is divided into two basic categories: sleeve gastrectomy and intestinal bypass, including duodenojejunal bypass, Roux-en-Y gastric bypass, or biliopancreatic diversion. There were no

differences between the two groups in the composition of surgery type, surgery, or recovery time.

Table 3 shows the number of patients with PONV and rescue antiemetics during each time interval. Significantly fewer patients in Group D had nausea and needed antiemetic medication in the PACU and for 2 h following discharge. After 2 h, there were no differences between the two groups. The overall incidence of vomiting was low and showed no difference between groups throughout the whole period.

Table 4 shows the maximum and average pain scores over time. Both maximum and average pain scores were significantly low in the PACU, and at 2 h and 2–6 h after PACU discharge in Group D. There were no differences between the two groups after 6 h. In addition, the number of patients requiring rescue pain medication and antiemetic agent was significantly lower in the PACU in Group D. There were no differences between the groups after PACU discharge, but the difference in PACU led to an overall reduction in number of patients requiring rescue pain medication in Group D.

Figure 1. STROBE flow diagram.



ICU, intensive care unit. PCA, patient controlled analgesia.

Table 1. Patient characteristics

	Group D (<i>n</i> = 76)	Group R (<i>n</i> = 58)	<i>P</i> -value
Age (years)	40.1 (11.5)	37.1 (10.1)	0.126
Sex (male/female)	28/48	17/41	0.360
Height (cm)	167.0 (8.7)	165.1 (8.3)	0.943
Weight (kg)	107.7 (18.6)	105.3 (18.9)	0.681
BMI (kg·m ⁻²)	38.4 (5.0)	38.5 (5.6)	0.378
ASA physical status (II/III)	38/38	32/26	0.553
Hypertension	40	25	0.274
Diabetes	28	16	0.258
Smoking (no/yes)	54/22	39/19	0.635

Continuous values are shown as the mean (SD). Categorical variables are expressed as number of patients. ASA, American Society of Anesthesiologists. BMI, body mass index.

Table 2. Surgery and recovery characteristics

	Group D (<i>n</i> = 76)	Group R (<i>n</i> = 58)	<i>P</i> -value
Type of surgery (SG/IB)	65/11	49/9	0.867
Duration of surgery (min)	105.0 (95.0–123.8)	105.0 (83.8–120.0)	0.369
Duration of anesthesia (min)	145.0 (135.0 -170.0)	147.5 (123.8–170.0)	0.428
Duration of PACU stay (min)	33.0 (27.3–42.3)	35.0 (29.8–43.5)	0.319
Postoperative hospital stay (days)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	0.516

Continuous values are shown as the median (25th–75th percentile). Categorical variables are expressed as number of patients. IB, intestinal bypass; PACU, postanesthesia care unit; SG, sleeve gastrectomy.

Table 3. Incidence of postoperative nausea, vomiting, and antiemetic administration

	Group D (<i>n</i> = 76)	Group R (<i>n</i> = 58)	<i>P</i> -value
Nausea			
PACU	2 (2.6%)	10 (17.2%)	0.005
PACU–2 h	5 (6.6%)	13 (22.4%)	0.010
2–6 h	16 (21.1%)	16 (27.6%)	0.418
6–24 h	37 (48.7%)	26 (44.8%)	0.658
24–48 h	21 (27.6%)	21 (36.2%)	0.348
Overall	46 (60.5%)	38 (65.5%)	0.592
Vomiting			
PACU	1 (1.3%)	3 (5.2%)	0.316
PACU–2 h	0 (0.0%)	2 (3.4%)	0.186
2–6 h	3 (3.9%)	4 (6.9%)	0.466
6–24 h	9 (11.8%)	5 (8.6%)	0.546
24–48 h	4 (5.3%)	2 (3.4%)	0.698
Overall	14 (18.4%)	10 (17.2%)	1.000
Incidence of antiemetic administration			
PACU	2 (2.6%)	7 (12.1%)	0.040
PACU–2 h	4 (5.3%)	9 (15.5%)	0.075

2–6 h	12 (15.8%)	9 (15.5%)	1.000
6–24 h	29 (38.2%)	15 (25.9%)	0.133
24–48 h	12 (15.8%)	8 (13.8%)	0.811
Overall	37 (48.7%)	27 (46.6%)	0.862

Values are presented as number of patients (%). PACU, post-anesthesia care unit.

Table 4. Postoperative pain scores (11-point NRS) and incidence of rescue analgesic administration

	Group D (<i>n</i> = 76)	Group R (<i>n</i> = 58)	<i>P</i> -value
Maximum NRS			
PACU	5.2 (2.4)	6.9 (1.4)	< 0.001
PACU–2 h	3.7 (1.1)	4.4 (1.5)	0.003
2–6 h	3.6 (1.2)	4.3 (1.5)	0.009
6–24 h	4.3 (1.5)	4.0 (1.4)	0.267
24–48 h	3.6 (1.2)	3.7 (1.3)	0.623
Mean NRS			
PACU	3.8 (1.6)	5.1 (1.2)	< 0.001
PACU–2 h	3.5 (0.9)	4.0 (0.9)	0.010
2–6 h	3.4 (0.8)	3.8 (1.1)	0.004
6–24 h	3.4 (0.6)	3.4 (0.6)	0.967
24–48 h	3.0 (0.4)	3.1 (0.5)	0.698
Incidence of analgesic administration			
PACU	49 (64.5%)	55 (94.8%)	< 0.001
PACU–2 h	17 (22.4%)	21 (36.2%)	0.078
2–6 h	15 (19.7%)	17 (29.3%)	0.244
6–24 h	39 (51.3%)	21 (36.2%)	0.081

24–48 h	17 (22.4%)	13 (22.4%)	0.995
Overall	63 (82.9%)	57 (98.3%)	0.004

NRS values are shown as the mean (SD). Incidence of analgesic administration is expressed as number of patients (%). NRS, numerical rating scale.

Discussion

We found that PONV and pain after bariatric surgery can be reduced through opioid-restricted TIVA using dexmedetomidine compared to opioid-included TIVA using remifentanyl. Some conflicting evidence has been reported regarding the benefits of opioid-free anesthesia in bariatric surgery in various anesthetic settings. For example, it seems that use of dexmedetomidine as an adjunct to volatile anesthetics reduces PONV, antiemetic requirement, postoperative pain, and rescue pain medication requirement compared to remifentanyl or fentanyl.[10, 12] In the case of intravenous anesthesia, Ziemann-Gimmel reported that opioid-free TIVA reduced the incidence and severity of PONV assessed in the morning on POD 1.[13] By contrast, another study showed that TIVA with propofol and dexmedetomidine reduced opioid requirement in the PACU, but did not reduce the incidence of PONV.[11] However, in these two studies, opioid-free TIVA was compared to anesthesia using volatile-based opioids. This could be a major confounding factor because TIVA is a known prophylactic measure for PONV compared to volatile anesthesia. By contrast, in the present study, TIVA was used in both groups, allowing us to assess the effects of opioid-free anesthesia without such confounding factors.

In our study, dexmedetomidine was used for intraoperative analgesia as a

substitute for remifentanyl. Therefore, the PONV-reducing effect in the opioid-restricted anesthesia group can be explained by two factors: exclusion of remifentanyl and addition of dexmedetomidine. Remifentanyl is an ultra-short-acting μ -opioid receptor agonist with a consistently short context-sensitive half-life. This trait has raised questions regarding whether intraoperative remifentanyl administration induces PONV similar to other opioid analgesics. Some studies have suggested that intraoperative remifentanyl does not increase PONV or result in a lower incidence of PONV compared to fentanyl[14-17] or alfentanil.[18-22] It has also been reported that remifentanyl increases PONV in a dose-dependent manner.[23] On the other hand, the PONV-reducing effects of dexmedetomidine can be mainly explained by the indirect effects of sparing opioid and inhaled anesthetic agents, although some groups have suggested that α -2 agonists may directly contribute to PONV reduction by decreasing catecholamine levels and sympathetic tone.[24, 25] Our results support the suggestion that replacement of remifentanyl with dexmedetomidine could be beneficial in populations at high risk for PONV, at least during the immediate postoperative period.

In Group D, a possible confounding factor was the use of a bolus dose of alfentanil to alleviate intubation stimulation; therefore, the anesthetic regimen was not completely opioid-free. However, alfentanil was administered as a single dose only during induction. In addition, alfentanil has very low potency

compared to remifentanyl (1:20–1:30).[26] Considering the terminal elimination half-life of alfentanil of 111 minutes and average anesthesia time in Group D of 145 minutes, it was highly unlikely that alfentanil influenced the incidence of PONV.[27] However, alfentanil could be replaced by bolus doses of other drugs, such as propofol, to achieve opioid-free anesthesia in future studies.

By subdividing the evaluation time, we examined when PONV occurred most frequently in bariatric surgery and for how long it can be affected by the anesthetic management. About 60% of the patients developed PONV within 0–24 h, and the incidence decreased by half within 24–48 h, but was still high at around 30%. The PONV-reducing effect lasted for up to 2 h after PACU discharge, but failed to significantly affect the overall incidence. This seemed to have been largely because the opioid-restricted protocol was only applied intraoperatively, which allowed administration of opioid analgesics without limitation after patients had entered the PACU.

Overall, a very high incidence of PONV was observed in both groups, even after triple prophylaxis with dexamethasone, ramosetron, and total intravenous anesthesia. This is consistent with previous studies indicating that bariatric surgical patients are not only susceptible to PONV but also appear to be less responsive to traditional PONV prophylaxis using TIVA or antiemetic

agents.[3, 4, 28, 29] The estimated causes of the high incidence of PONV after bariatric surgery can be divided into patient factors and surgical factors. First, high-risk patients, such as women and younger patients, account for a large proportion of patients undergoing bariatric surgery.[30] Second, in addition to laparoscopic surgery being a known risk factor for PONV, many surgical factors can also cause PONV.[31] Biochemically, it has been suggested that intraoperative gastric manipulation triggers emesis by stimulating the enterochromaffin cells of the stomach to secrete 5-hydroxytryptamine.[5, 28, 32] Surgical injuries to the stomach and gastric vagal afferent branches can decrease gastric motility.[5, 33] Furthermore, bariatric surgery is a restrictive surgery that reduces gastric volume and increases intragastric pressure, which can also contribute to PONV after commencement of oral diet.[6] With regard to specific categories of bariatric surgery, sleeve gastrectomy has a higher incidence of PONV than Roux-en-Y gastric bypass, which can be explained by delayed gastric emptying depending on whether the pylorus is preserved.[5, 29] In this study, the proportion of patients undergoing sleeve gastrectomy was large, which may have contributed to the observed high incidence of PONV.

The pain score significantly decreased until 6 h after PACU discharge in Group D. The significant reduction of pain score immediately after surgery may have been attributable to the analgesic effects of dexmedetomidine itself and prevention of opioid-induced hyperalgesia through exclusion of remifentanyl.

The incidence of rescue analgesic requirement was significantly decreased in the PACU (from about 95% to 65%), which led to a significant reduction in overall incidence. However, rescue analgesic agents were eventually administered in 90% of all patients despite use of intravenous fentanyl PCA, which raises the question of whether the postoperative pain control was appropriate. Bolus-only PCAs were used in all except three patients in Group D and one patient in Group R to reduce the side effects of continuous infusion of opioids. Nevertheless, a significant number of patients turned off their PCA devices intermittently due to PONV, which led to use of other types of rescue pain control, mainly consisting of opioid analgesics. This implies that the management of PONV and effective pain control are interactive.

Our findings suggest that a multidisciplinary approach to pain control while reducing PONV not only in the operating room, but also in the postoperative period, is essential in this patient group. Pain control by combination or replacement of regimens using non-opioid analgesic agents, and other multimodal analgesic measures, such as transversus abdominis plane (TAP) block and epidural analgesia could be applied. As not only anesthetic components but also the characteristics of the surgical procedure and diet resumption can contribute to PONV, more intense and prolonged antiemetic regimens should be included in the postoperative care protocols.

This study had some limitations. First, because of the retrospective nature of the study, some information that could have been helpful in interpreting the results could not be obtained, such as the severity of PONV, the patients' previous history of PONV or motion sickness, the dose of fentanyl PCA used during each time interval, and so forth. Second, as PONV was detected by a review of the medical records, the incidence may have been underestimated. However, in cases of undocumented PONV, it is possible that it may have been minor and did not cause serious discomfort to the patient or require treatment.

Conclusion

Opioid-restricted total intravenous anesthesia using dexmedetomidine reduces PONV, pain score, and rescue antiemetic and analgesic requirements in the immediate postoperative period after bariatric surgery.

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국 문 초 록

연구 배경. 수술 후 오심 및 구토는 비만대사수술 후 호발하며 회복 지연, 수술 부작용, 재입원 및 의료 비용 증가를 유발한다. 본 연구는 레미펜타닐을 대신하여 텍스메데토미딘을 사용하는 아편유사제 제한 전정맥마취가 비만대사수술 환자에서 수술 후 오심 및 구토의 빈도를 감소시킬 수 있는지 후향적으로 조사하였다.

연구 방법. 2019년 1월부터 12월 사이에 전정맥마취 하 정규 복강경 비만대사수술을 받은 성인 환자의 전자 의무 기록을 검토하였다. 환자들은 마취에 사용된 약제에 따라 텍스메데토미딘 군과 레미펜타닐 군으로 분류되었다.

연구 결과. 총 134명의 환자가 분석에 포함되었다. 수술 후 오심의 빈도는 마취회복실 퇴실 후 2시간까지 레미펜타닐 군보다 텍스메데토미딘 군에서 유의하게 낮았다. (마취회복실에서 $P = 0.005$, 마취회복실 퇴실 후 2시간까지 $P = 0.010$) 수술 후 통증 점수는 마취회복실 퇴실 후 6시간까지 텍스메데토미딘 군에서 유의하게 낮았다. 또한, 마취회복실에서 항구토제 및 진통제 투여 빈도는 텍스메데토미딘 군에서 유의하게 낮았다.

결론. 텍스메데토미딘을 사용한 아편유사제 제한 전정맥마취는

비만대사수술 직후에 수술 후 오심 및 구토, 통증 점수, 항구토제
및 진통제 요구량을 감소시킨다.

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주요어: 비만대사수술, 텍스메데토미딘, 수술 후 오심 및 구토

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