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Original Contribution

Comparison of intravenous ibuprofen and acetaminophen for postoperative multimodal pain management in bariatric surgery: A randomized controlled trial☆,☆☆,☆☆☆

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ABSTRACT

Study objective: Multimodal analgesic strategies are recommended to decrease opioid requirements and opioid-induced respiratory complications in patients undergoing laparoscopic bariatric surgery. Recent studies have demonstrated that intravenous ibuprofen decreases opioid consumption compared with placebo. The primary aim of this study was to compare the effect of intravenous ibuprofen and intravenous acetaminophen on opioid consumption. We also aimed to compare postoperative pain levels and side effects of the drugs.

Design: Randomized, double-blinded study.

Setting: University hospital.

Patients: Eighty patients, aged 18–65 years, (ASA physical status II-III) undergoing laparoscopic sleeve gastrectomy or laparoscopic Roux-en-Y gastric bypass surgery were included in this study.

Interventions: Patients were randomized to receive 800 mg ibuprofen or 1 g acetaminophen intravenously every 6 h for the first 24 h following surgery; in addition, patient-controlled analgesia with morphine was administered.

Measurements: Postoperative morphine consumption in the first 24 h, visual analog scale (VAS) pain scores at rest and with movement, and opioid related side effects were assessed. In addition, time to passage of flatus, surgical complications, lengths of intensive care unit and hospital stay, and laboratory parameters were recorded.

Main results: The mean morphine consumption was 23.94 ± 13.89 mg in iv ibuprofen group and 30.23 ± 13.76 mg in the acetaminophen group [mean difference: -6.28 (95% CI, −12.70, 0.12); $P = 0.055$]. The use of intravenous ibuprofen was associated with reduction in pain at rest (AUC, 1- to 24-h, $P < 0.001$ and 12- to 24-h, $P = 0.021$) and pain with movement (AUC, 1–24, 6–24, and 12–24 h, $P < 0.001$). Intravenous ibuprofen was well tolerated with no serious side effects except dizziness.

Conclusions: Intravenous ibuprofen did not significantly reduce opioid consumption compared to intravenous acetaminophen; however, it reduced the severity of pain. Intravenous ibuprofen may be a good alternative to intravenous acetaminophen as part of a multimodal postoperative analgesia in patients undergoing bariatric surgery.

1. Introduction

Obesity is a chronic disease that adversely affects the quality of life and longevity and is one of the most important health problems of today. Bariatric surgery is a highly effective method to maintain weight loss in morbidly obese patients thereby improving the quality of life and life expectancy [1]. Along with the increase in incidence of obesity, an increasing number of laparoscopic bariatric surgeries are being performed every year.

Currently, despite improved knowledge about nociception and

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advances in pharmacology, 80% of surgical patients report moderate, and 31–37% severe to intolerable postoperative pain [2]. Similarly, in patients undergoing laparoscopic bariatric surgery, 41% of patients experienced severe postoperative pain in the first 48 h [1]. Insufficient control of postoperative pain leads to serious complications including delayed wound healing, impaired gastrointestinal motility, myocardial ischemia, immunologic changes, pulmonary complications, and increased risk of thromboembolism due to immobility [1–3].

The use of centrally acting opioids is the cornerstone of management of severe postoperative pain; however, their side effects have evinced increasing interest on opioid sparing multimodal analgesic strategies [2]. Similarly, opioid-sparing multimodal analgesia strategies are becoming more important in morbidly obese patients with concomitant co-morbidities and specific problems related due to anesthesia and surgery [1, 4–6].

Acetaminophen is one of the most widely used analgesic drugs due to its good tolerance and high safety profile. Though the intravenous (iv) use of acetaminophen has increased in the perioperative period, similar to opioids it has only central effect. It has been reported that iv acetaminophen use in bariatric surgery reduces morphine consumption and length of hospital stay compared to placebo [7, 8].

I contrast to acetaminophen and opioid, nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the sensitization of pain receptors by blocking the inflammatory cascade that occurs during surgery. With peripheral anti-inflammatory activity, they facilitate a reduction in the opioid dose and improve recovery.

Ibuprofen is a propionic acid derivative with anti-inflammatory, analgesic, and antipyretic properties similar to other NSAIDs that are non-specific inhibitors of cyclooxygenase (COX) enzymes [2]. Iv form was launched in the USA in 2009 and the first generic form was approved in 2015 in Turkey. In a few placebo-controlled studies in patients undergoing orthopedic and abdominal surgery, postoperative analgesia with an opioid sparing effect has been demonstrated [9–12]. To our knowledge, there is no data on the use of iv ibuprofen in bariatric surgery.

We hypothesized that iv ibuprofen may be advantageous as a part of multimodal analgesic strategy compared to iv acetaminophen, due to its central and peripheral analgesic activity in this high-risk group of patient, where the postoperative pain control is important and still controversial. The primary aim of this randomized, double blind study was to compare the efficacy of iv ibuprofen with iv acetaminophen based on opioid consumption. The secondary aim was to compare postoperative pain levels, and side effects, in morbidly obese patients undergoing bariatric surgery.

2. Materials and methods

The study was carried out between January 2016 and January 2017 following Ethics Committee approval (Ethics Committee No: 2015/191) and written informed consent from patients. This study was registered with ClinicalTrials.gov (NCT02778958) in May 2016. Obese patients aged 18–65 years, ASA (American Society of Anesthesiology) physical status II-III, scheduled for laparoscopic sleeve gastrectomy or laparoscopic Roux-en-Y gastric bypass surgery were included in this parallel group, randomized (in a 1:1 ratio), and double-blinded (treatment assignment was blinded) study. Patients with hepatic dysfunction, renal insufficiency [creatinine > 3 mg/dL or creatinine clearance < 60 mL/min or oliguria (urine output < 500 mL/day) or history of dialysis 28 days before surgery], history of gastrointestinal bleeding or hemorrhagic diathesis, full-dose anticoagulant use (excluding prophylactic subcutaneous heparin), use of angiotension-converting enzyme inhibitor and furosemide combination, opioid addiction or tolerance, patients with history of allergy to the study drugs, and patients unable to cooperate for pain assessment were excluded from the study.

All patients were instructed about the use of patient-controlled analgesia (PCA) and pain assessment scales preoperatively. Routine aspiration prophylaxis was administered with an H_2 receptor blocker, metoclopramide, and a proton pump inhibitor. Patients were transferred to the operating room without sedative premedication and were admitted to the operating table in the ramp position. In addition to routine monitoring, invasive arterial monitoring was performed. Venous access was established with two wide-bored cannulae. A central venous catheter placement was planned in patients who had difficult venous access or comorbid disease. After preparation for difficult airway, rapid-sequence intubation was carried out with 2 mg/kg propofol (according to lean body weight) and 1 mg/kg rocuronium (according to ideal body weight) followed by preoxygenation with 100% O_2. Iv morphine, 50 μg/kg, was administered before the incision. Anesthesia was maintained with 6–8% desflurane in O_2/air (fraction of inspiratory O_2: 50–60%) and remifentanil infusion at 0.05–0.1 μg/kg/min (according to ideal body weight) titrated to effect, based on the hemodynamic status. At the end of the surgery, the muscle relaxant effect was reversed with 2–4 mg/kg sugammadex and patients were extubated.

The research director randomly assigned patients into two groups. A blocked randomization scheme (80 subjects randomized into 20 blocks) was generated by through the web site Randomization.com (http://www.randomization.com). Patients in Group I received iv ibuprofen (Intrafen®, Gen Ilac, Istanbul, Turkey) 800 mg in 200 mL saline, and patients in Group A received iv acetaminophen (Perfalgan®, Bristol-Myers Squibb, Anagni, Italy) 1 g. A total of four doses were administered as a slow infusion. The first dose was administered 30 min before skin closure, followed by a repeat dose every 6 h for the first 24 h. Study drugs were prepared by a nurse anesthesiologist in a black sheath not to recognize, and were administered by a member of the research team. The patient, surgical team, and the anesthesiologist who collect postoperative data were blinded to the study drugs.

Postoperative pain intensity was measured by patient self-assessment, using a visual analogue scale (VAS) from 0 to 100 (0 = no pain and 100 = the worst pain imaginable) at rest and with movement. Pain with movement was standardized as assuming the sitting position from a supine position. In the recovery room, only the VAS score at rest was assessed regarding patient comfort; if the score was ≥40, 1 mg morphine was administered intravenously until the pain subsided, up to maximum of two doses. After 30 min of stay in the recovery room, patients were commenced on iv morphine PCA with 1 mg bolus and 20 min lockout time, and transferred to the intensive care unit. Patients were managed in the intensive care unit until they were stable and then transferred to the surgical ward.

Morphine consumption and VAS levels were followed at postoperative 1st, 2nd, 4th, 6th, 12th, 18th and 24th hours. If the VAS score was ≥40 during the PCA lock-out period and if none of the study drugs were due to be administered, 0.5 mg /kg tramadol was planned as a rescue analgesic. Mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SpO_2) were recorded postoperatively. Patients were followed up for nausea, vomiting, sedation, headache, itching, dyspepsia, respiratory depression, and pulmonary complications. The level of sedation was evaluated with the Ramsay sedation score (1, awake and anxious, agitated, or restless; 2, Awake, cooperative, orientated, and tranquil; 3, Responds only to commands; 4, asleep, brisk response to stimulus; 5, asleep, sluggish response to stimulus; 6, no response). Patient satisfaction was assessed using a triple scale (1, not satisfied; 2, satisfied; 3, very satisfied) at 6 and 24 h postoperatively. The time to passage of flatus, surgical complications, and length of intensive care unit and hospital stay were followed up and recorded postoperatively. In addition, laboratory parameters preoperatively and on the second postoperative day were recorded. An anesthesiologist who was unaware of the study groups carried out all follow-ups.

The primary outcome of the study was the total amount of morphine consumption during the 24-h postoperative period. Mean and standard deviation of morphine consumption from a previously completed study

were used to calculate the sample size (SD 12.8) [8]. Power analysis was performed using $\alpha = 0.05$ and $1\text{-}\beta = 0.90$ with two-sample (independent) *t*-test; we calculated a sample size at least 35 subjects in each group to demonstrate an average difference of morphine consumption of 10 mg (30% reduction). Considering study withdrawals or protocol violation, we set a sample size of 40 in each arm.

We used SPSS (Statistical Package for Social Sciences) for Windows version 22.0 software and SAS® PROC GLM, Version SAS Studio 3.6 University Edition for all statistical analyses. Repeated measures ANOVA with Bonferroni multiple comparison tests was applied for repetitive measurements of VAS score. To determine the difference in overall pain at different time points, the area under the VAS pain curve (AUC) was analyzed during the first 24 h, between 6 and 24 h, and between 12 and 24 h. Quantitative data were presented as mean, median, least squares means, and the difference in means with 95% confidence interval; qualitative data were presented number and percentage. The Shapiro Wilk normality test was used to test whether quantitative variables showed a normal distribution. For statistical evaluation of quantitative variables with normal distribution, the paired *t*-test and the unpaired *t*-test were used; the Wilcoxon test and Mann-Whitney *U* test were used for non-quantitative variables. Statistical evaluation of qualitative variables was performed by Pearson Chi-square analysis and Fisher's exact Chi-square analysis. A *P* value of < 0.05 was considered statistically significant.

3. Results

A total of 80 patients were randomized into two groups. In Group I, one patient was excluded due to an allergic reaction that occurred at 4 h postoperatively and four patients were excluded due to protocol violation. In Group A, 1 patient was excluded due to postoperative intestinal perforation (Fig. 1). There was no difference between groups regarding age, gender, body mass index (BMI), ASA status, and comorbidities. Five patients in Group I and six patients in Group A had obstructive sleep apnea syndrome (OSAS) diagnosed by polysomnography. The duration of surgery, the type of surgical procedures, and intraoperative remifentanil consumption were similar between groups (Table 1).

In recovery room, four patients received 1 mg and 19 patients received 2 mg morphine (total 23 patients) in Group I. In Group A, nine patients were given 1 mg, and 19 patients were administered 2 mg morphine (total 28 patients). There was no significant difference between groups regarding the number of patients who received morphine ($P = 0.45$) and the total amount of morphine administered in recovery room ($P = 0.22$).

At 24 h postoperatively, the total morphine consumption was 23.94 ± 13.89 mg in Group I and 30.23 ± 13.76 mg in Group A [mean difference = −6.28 (95% CI, −12.70, 0.12); $P = 0.055$] (Table 2). The use of iv ibuprofen was associated with reduction in pain at rest (AUC, 1–24 h, $P < 0.001$ and 12–24 h, $P = 0.021$) and pain with movement (AUC, 1–24, 6–24, and 12–24 h, $P < 0.001$) compared with acetaminophen group (Table 3). Two patients in Group A required rescue treatment with tramadol while in Group I, no rescue treatment was required.

There was no difference between groups regarding postoperative MAP, HR, and SpO_2 levels (Figs. 2, 3, 4). The frequency of nausea-vomiting, antiemetic consumption, sedation level, headache, itching, and dyspepsia frequency was similar between groups. No respiratory depression was encountered in any patient (Table 4). In Group I, one patient developed an urticarial rash at the postoperative 4th hour, hence morphine PCA was terminated and antihistamines and steroids were administered. Another patient developed dyspnea and fever due to atelectasis on the 2nd postoperative day. This patient was administered continuous positive airway pressure (CPAP) and was discharged without any problems on the 4th postoperative day. In another patient, dyspnea and left pleural effusion were noted on the 3rd postoperative day. The clinical course of this patient was complicated by empyema, which was treated with tube thoracostomy and broad-spectrum antibiotics and eventually, the patient was discharged home. In Group A, postoperative CPAP was administered due to respiratory distress in two patients with preoperative diagnosis of OSAS and CPAP use. Diagnostic laparoscopy was performed for acute abdomen pain on another patient in Group A on the 2nd postoperative day. Intestinal perforation was detected and treated with primary closure. The mean time (hours) for the first passage of flatus was shorter in Group I than Group A (35.06 ± 13.2 vs 43.20 ± 13.85, $P = 0.02$).

Patient satisfaction levels were higher in Group I at 6th hour postoperatively ($P = 0.01$); however, there was no difference between the two groups at 24th hour ($P > 0.05$). There was no difference between groups regarding duration intensive care and hospital stay (Table 4). There was no difference within or between groups in the pre and postoperative laboratory parameters (Table 5).

4. Discussion

There are few studies related to the use of iv ibuprofen for postoperative pain relief. In a three-armed randomized controlled trial by Southworth et al. in 2009, 406 patients who underwent orthopedic and abdominal surgery received either 400 mg or 800 mg of iv ibuprofen, or placebo for a total of eight doses. In the group that received 800 mg ibuprofen, there was a significant decrease in opioid use (26%) compared to placebo, and lower pain levels were observed; opioid use was not significantly different with ibuprofen 400 mg compared to placebo [9]. Singla et al. observed 30.9% reduction in opioid consumption compared to placebo and a significant decrease in pain levels ($P < 0.001$) with iv ibuprofen in a study of 185 adult patients undergoing elective orthopedic surgery [10]. In a study including 319 patients who underwent abdominal hysterectomy, Kroll et al. found that 800 mg iv ibuprofen resulted significant reduction in pain levels and opioid consumption compared to the placebo group (19%) and facilitated earlier ambulation [11]. In a multicentric placebo-controlled study of 206 patients who underwent abdominal and orthopedic surgery, 800 mg iv ibuprofen resulted in significant reduction in opioid consumption (52%) and lower levels of pain [12]. In all these studies, the dosage and protocol for iv ibuprofen use were similar to those used in our study; however, comparisons were made with placebo instead of acetaminophen.

The high incidence of OSAS and other comorbidities in morbid obesity increase the susceptibility to opioid-induced respiratory complications including airway obstruction, and this increases concerns about the liberal use of opioids with high ceiling effects [4]. Hence, we did not include a placebo arm in our study due to concerns regarding risks associated with increased opioid consumption and respiratory complications. Iv ibuprofen was directly compared with iv acetaminophen, the efficacy of which has been demonstrated in bariatric surgery as a component of opioid-sparing multimodal analgesia [8, 13–15]. Moreover, we used a different iv morphine PCA protocol as our patient population was different; due to heavy sedation and mobility problems encountered previously with standard iv morphine PCA protocol (2 mg bolus with a lockout time of 5–10 min), we preferred the routine protocol used in our clinic for bariatric surgery (1 mg bolus with a lockout time of 20 min).

McDaid et al., in their meta-analysis of 60 studies, compared the effects of three different classes of nonopioid analgesics (acetaminophen, NSAIDs and COX-2 selective inhibitors) on morphine consumption and morphine-related side effects. They found lower morphine consumption with NSAIDs and COX-2 inhibitors compared to acetaminophen. However, they concluded that this difference was small, and not clinically significant after adjustment according to basal morphine consumption. Besides, only five studies directly compared NSAIDs with acetaminophen in this meta-analysis and, different types of NSAIDs were grouped together [16]. It has been reported that the

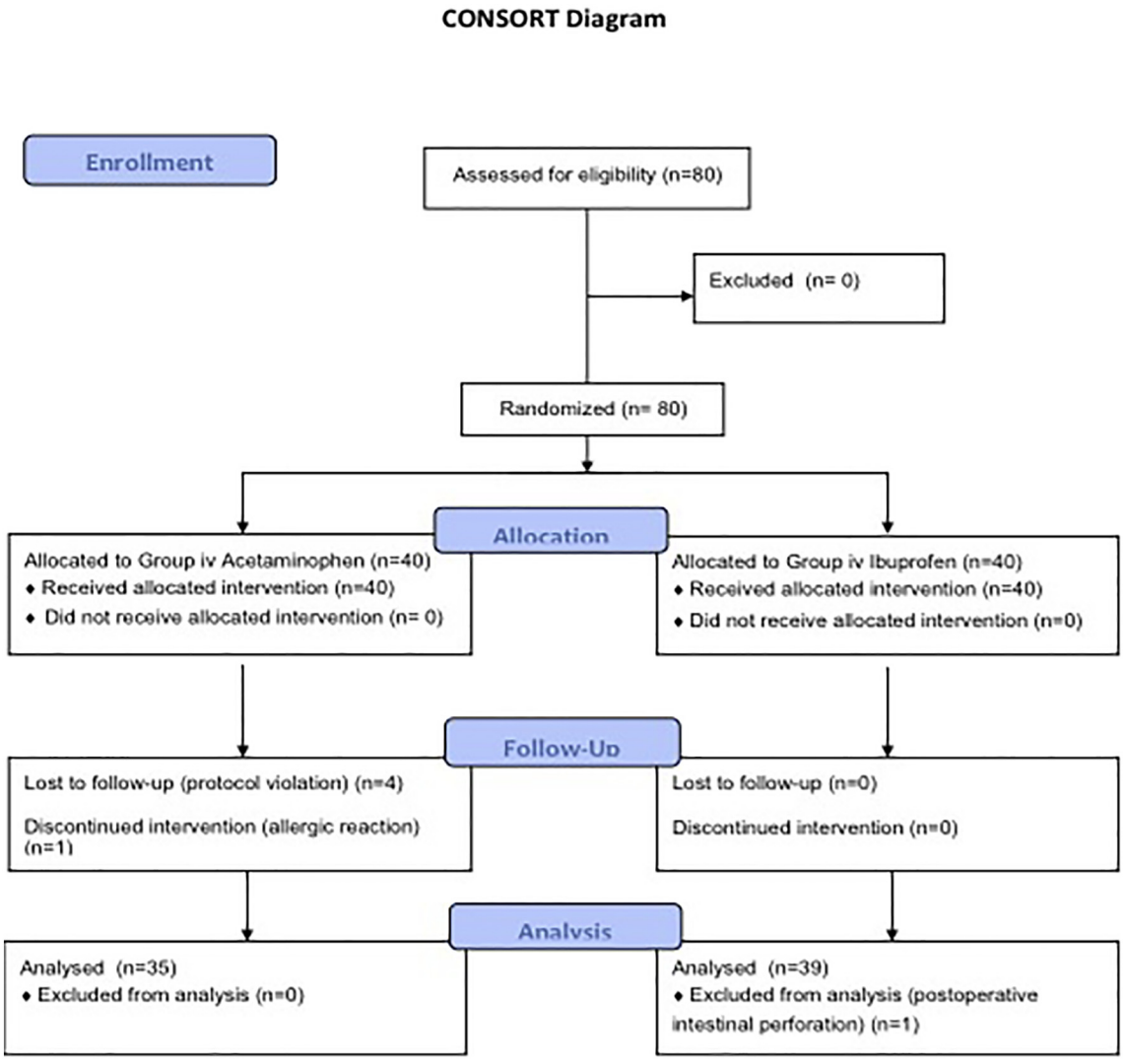

Fig. 1. Flow diagram.

Table 1
Demographic characteristics and surgical data [mean ± standard deviation, or number (%), or median (min-max)].

	Group I (n = 35)	Group A (n = 39)
Age (year)	37.82 ± 11.94	39.41 ± 9.85
Gender (female/male)	23/12	24/15
Weight (kg)	125.12 ± 20.31	125.62 ± 17.74
Height (cm)	164.94 ± 10.11	166.15 ± 10.37
BMI (kg/m^2)	45.79 ± 4.41	45.44 ± 4.66
ASA (II/III) classification	24/11	32/7
Preoperative comorbidities		
Hypertension	8 (22.9%)	11 (28.9%)
Diabetes mellitus	11 (31.4%)	8 (21.1%)
Coronary artery disease	3 (8.6%)	0
OSAS	5 (14.3%)	6 (%15.4)
Duration of surgery (min)	180.66 ± 54.19	193.54 ± 60.69
Operation type		
Sleeve gastrectomy/ Roux-en-Y-gastric bypass	18/17	18/21
İntraoperative remifentanyl consumption	370.58 ± 367.03 310 (40–2000)	300.40 ± 364.05 200 (30–1800)

BMI: Body mass index; ASA: American Society of Anesthesiology; OSAS: Obstructive sleep apnea syndrome.

Table 2
Morphine consumption in the 24-h postoperative period.

	Group I (n = 35)	Group A (n = 39)
Mean ± SD (mg)	23.94 ± 13.88	30.23 ± 13.76
95% CI of means	19.17–28.71	25.77–34.69
Difference in means with 95% CI	−6.28 (−12.70, 0.12)	

P value = 0.055; SD, standard deviation; CI, confidence interval.

reduction in morphine consumption vary with different types of NSAIDs compared to placebo (ranging from 4.8 to 16.7 mg) and their efficacy might be different [17]. In our study, although a 21% reduction in morphine consumption was observed in the ibuprofen group, there was no statistical difference between the two groups. However, this reduction in morphine consumption may be clinically significant for morbidly obese patients undergoing bariatric surgery. Improvement of pain levels is another important outcome in the preference of non-opioid adjuvants in multimodal analgesia [17]. In our study, pain levels at rest (except at one time period) and with movement (at all times period) were lower in the ibuprofen group. Pain with movement is often considered to be more severe than resting pain and may have clinically important consequences such as reduced mobilization, increasing the risk of postoperative complications including delirium, pneumonia,

Table 3
Summary of pain measured by visual analog scale (VAS) scores [0 − 100] at rest and with movement.

Score	Group I (n = 35)	Group A (n = 39)
Pain at rest (VAS-AUC)		
1–24 h		
Mean ± SD	28.73 ± 19.53	32.34 ± 22.43
LS mean ± SE	28.73 ± 0.79	32.74 ± 0.76
LS mean (95% CI)	27.17, 30.29	31.24, 34.25
LS mean difference (95% CI)	−4.01 (−6.17, −1.84)	
P	< 0.001	
6–24 h		
Mean ± SD	20.21 ± 14.76	22.17 ± 16.97
LS mean ± SE	20.21 ± 0.86	22.17 ± 0.82
LS mean (95% CI)	18.50, 21.92	20.55, 23.79
LS mean difference (95% CI)	−1.96 (−4.32, 0.39)	
P	0.101	
12–24 h		
Mean ± SD	18.28 ± 13.61	20.94 ± 15.86
LS mean ± SE	18.28 ± 0.83	20.94 ± 0.78
LS mean (95% CI)	16.64, 19.38	19.38, 22.49
LS mean difference (95% CI)	−2.65 (−4.91, −0.39)	
P	0.021	
Pain with movement (VAS-AUC)		
1–24 h		
Mean ± SD	35.53 ± 20.22	43.20 ± 22.23
LS mean ± SE	33.53 ± 0.84	43.75 ± 0.81
LS mean (95% CI)	31.87, 35.18	42.15, 45.35
LS mean difference (95% CI)	−10.22 (−12.53, −7.92)	
P	< 0.001	
6–24 h		
Mean ± SD	25.25 ± 16.17	33.71 ± 18.35
LS mean ± SE	25.25 ± 0.97	33.71 ± 0.92
LS mean (95% CI)	23.32, 27.17	31.89 ± 35.54
LS mean difference (95% CI)	−8.46 (−11.12, −5.81)	
P	< 0.001	
12–24 h		
Mean ± SD	11.33 ± 11.12	13.30 ± 12.08
LS mean ± SE	11.33 ± 0.35	13.07 ± 0.33
LS mean (95% CI)	10.64, 12.02	12.40, 13.73
LS mean difference (95% CI)	−1.73 (−2.69, −0.78)	
P	< 0.001	

The analysis is based on repeated measures ANOVA with Bonferroni multiple comparison test. SD, standard deviation; SE, standard error; LS, least squares; CI, confidence interval; AUC, area under the curve.

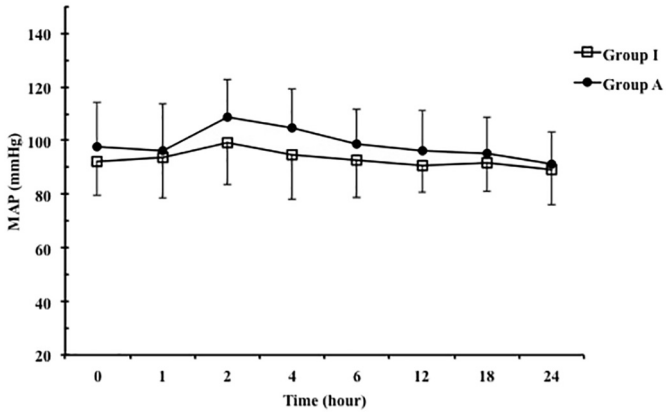

Fig. 2. Mean arterial pressure of groups at postoperative time points. Squares and circles indicate means and error bars indicate standard deviations.

bowel dysfunction, pulmonary atelectasis, and thromboembolic events [2]. Lower pain levels and relatively less opioid consumption might have led to earlier bowel function in the ibuprofen group, though we did not record the time to initial mobilization in our patients.

The analgesic effect of NSAIDs is explained by the pharmacological property of inhibiting prostaglandin biosynthesis, which leads to a

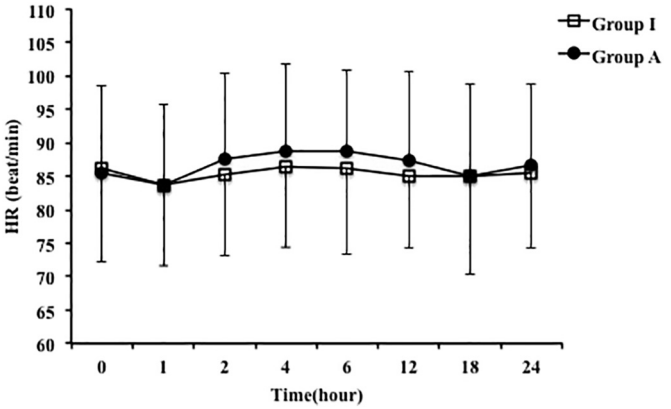

Fig. 3. Heart rate of groups at postoperative time points. Squares and circles indicate means and error bars indicate standard deviations.

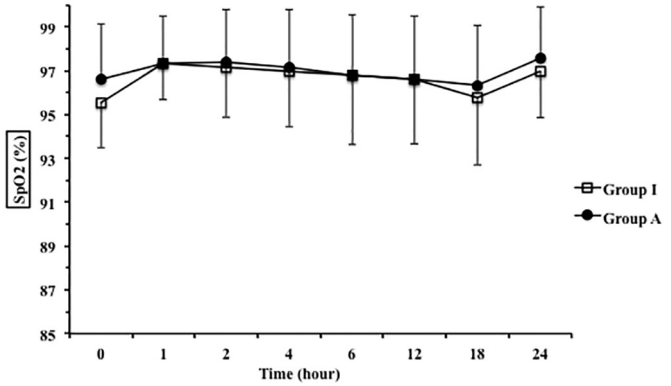

Fig. 4. Peripheral oxygen saturation of groups at postoperative time points. Squares and circles indicate means and error bars indicate standard deviations.

Table 4
Comparison of adverse events, patient satisfaction, and duration of ICU and hospital stay [number (%) or mean ± standard deviation].

	Group I (n = 35)	Group A (n = 39)	*P*
Nausea-vomiting	24 (68.6%)	28 (71.8%)	0.803
Antiemetic consumption	20 (57.1%)	25 (64.1%)	0.635
Ramsay sedation score (1/2/3/4/5/6)	1/34/0/0/0/0	0/37/2/0/0/0	0.348
Headache	7 (20%)	7 (17.9%)	0.822
Dizziness	15 (42.9%)	6 (15.4%)	0.011
Pruritus	0	0	-
Dyspepsia	1 (2.9%)	7 (%17.9)	0.590
Respiratory depression	0	0	–
Patient satisfaction (1/2/3)			
At postoperative 6th hour	3/20/12	6/30/3	0.014*
At postoperative 24th hour	3/11/21	2/19/18	0.183
ICU time (hour)	33.37 ± 18.45	31 ± 10.7	0.895
Hospital length of stay (day)	4.25 ± 2.14	4.12 ± 20	0.765

Patient satisfaction (1, unsatisfied; 2, satisfied; 3, very satisfied) *$P < 0.05$.

reduction or reversal of peripheral sensitization, and also by suppressing prostanoid formation in the spinal cord and the brain, thus affecting central sensitization [18, 19]. Peripheral, spinal, and higher central nervous effects of ibuprofen may explain low pain scores in our study.

A potential synergistic effect may occur with the co-administration of iv ibuprofen and acetaminophen due to their central analgesic effects when used for postoperative pain relief. Gupta et al. compared iv ibuprofen alone with a combination with iv acetaminophen for knee and hip arthroplasty. They found a decrease in the use of opioids, fewer

Table 5
Laboratory findings (mean ± standard deviation).

		Group I (n = 35)	Group A (n = 39)	*P*
Preoperative	Hemoglobin (g/dL)	13.76 ± 1.42	14.36 ± 1.96	
	Platelet (10^3/μL)	312.20 ± 71.99	308.69 ± 75.50	
	INR	0.99 ± 0.10	0.98 ± 0.07	
	AST (U/L)	20.20 ± 6.83	24.76 ± 17.14	
	ALT (U/L)	25.58 ± 13.51	34.58 ± 25.67	
	BUN (mg/dL)	12.06 ± 4.29	12.43 ± 4.09	
	Serum creatinine (mg/dL)	0.73 ± 0.11	0.73 ± 0.13	
Postoperative	Hemoglobin (g/dL)	11.87 ± 1.53	12.57 ± 2.14	0.119
	Platelet (10^3/μL)	259.26 ± 78.75	249.15 ± 63.26	0.545
	INR	1.15 ± 0.11	1.16 ± 0.15	0.658
	AST (U/L)	95.70 ± 139.27	64.46 ± 59.05	0.206
	ALT (U/L)	111.67 ± 190.78	85.30 ± 70.22	0.424
	BUN (mg/dL)	10.20 ± 6.21	8.58 ± 6.52	0.284
	Serum creatinine (mg/dL)	0.70 ± 0.15	0.70 ± 0.20	0.948

INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urine nitrogen.

potential adverse events related to opioid use, and improved pain scores in the combination group [20]. Future studies on the co-administration of acetaminophen and ibuprofen in morbid obese patients undergoing bariatric surgery might be warranted.

One of the clinically important reasons for not preferring opioids is due to drug-related side effects [6, 17]. NSAID related gastrointestinal and cardiovascular side effects, and the risk of bleeding limit the long-term use of these drugs. For example, seven cases of gastric perforation due to long-term NSAID use after bariatric surgery have been reported [21]. Recently, a few studies have related the use of NSAIDs (especially diclofenac) with an increased risk of anastomotic leakage after colorectal surgery, leading to controversy [22, 23], however other studies do not corroborate with these findings [24, 25]. It has been suggested that similar risks exits with anastomoses of the small intestine and the stomach, and therefore further studies are needed in bariatric surgery [2]. NSAIDs are less preferred in bariatric surgery for multimodal analgesia, because of these risks, and there are few publications on this topic [5, 6, 8, 26].

Ibuprofen has a lower COX-1/COX-2 inhibition ratio (2.5:1) than other NSAIDs such as ketorolac (inhibition rate of COX-1 to COX-2 is 330:1) and side effects such as bleeding and gastrointestinal system are less frequent [13]. In the safety analysis study conducted by Southworth et al., it was reported that perioperative short-term use of ibuprofen, including colorectal surgery, was well tolerated. It has been suggested that iv ibuprofen is not associated with significant increase in adverse events compared with placebo, except for dizziness, especially with the 800 mg dose [18]. We also found in our study that dizziness was more frequent in the ibuprofen group than in the acetaminophen group, which may be attributable to a common central nervous system side effect of NSAIDs. Therefore, patients and caregivers need to be aware of this side effect.

It has been emphasized that the use of proton pump inhibitors with NSAIDs after bariatric surgery was protective against marginal ulceration [27, 28]. In our study, ibuprofen was used for a short time, and perioperative prophylaxis was performed with proton pump inhibitors. As a result, there were no postoperative complications such as anastomotic leak, gastric perforation or hemorrhage in the ibuprofen group.

Our study is limited by the inclusion of two different types of bariatric surgical procedures; analgesic requirement may be different with different procedures. We did not perform subgroup analysis because of the small sample size.

In studies conducted with non-opioid analgesics using a multimodal analgesic strategy, it has been suggested that a reduction in opioid-related complications was clinically more important than the reduction in opioid consumption [6, 17]. Our sample size was not sufficient to derive a conclusion about the incidence of opioid-related side effects.

Administration of 800 mg iv ibuprofen for the management of postoperative pain in morbidly obese patients undergoing bariatric surgery did not significantly reduce opioid consumption compared to iv acetaminophen; however, it resulted in reduced severity of pain. No serious side effects were observed and iv ibuprofen was well tolerated, except for dizziness; however, our sample size was insufficient to derive firm conclusion. Iv ibuprofen may be a good alternative to iv acetaminophen as part of a multimodal postoperative analgesic strategy in this high-risk group of patients, for whom postoperative pain control is important and controversial.

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