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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