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Effect of preoperative oral paracetamol as a part of multimodal analgesia for patients undergoing laparoscopic bariatric surgery

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Abstract

Nowadays, bariatric procedures are performed via laparoscopy. Nonetheless, many patients report distressing postoperative pain. Although opioids significantly reduce that sensation, it has numerous drawbacks in such cases as respiratory depression. Pre-emptive administration of other analgesics is associated with significant analgesic benefits with a reduction in opioid requirement. Paracetamol is a widely used and available analgesic. The benefits of intravenous pre-emptive administration were extensively discussed, with few studies reporting the effect of oral pre-emptive administration. That is why we conducted this research to elucidate if oral paracetamol could have analgesic benefits in individuals scheduled for bariatric surgery. Seventy subjects admitted for laparoscopic bariatric procedures were enrolled in our randomized prospective trial; Group I received oral paracetamol 1 gm one hours before the operation, whereas Group II received a placebo. The duration of the procedure, isoflurane consumption, and perioperative hemodynamic parameters did not show notable differences between the study groups. The intensity of postoperative pain decreased significantly in the paracetamol group during the initial 45 minutes after the operation. Additionally, pre-emptive paracetamol administration led to a significant delay in the first call for rescue analgesia (45 vs. 30 minutes in the placebo group) as well as a marked reduction in opioid consumption (40 vs. 80 mg in the placebo group). Postoperative adverse events had comparable incidences between the two groups, and all patients showed almost similar mobilization time and hospitalization period. Pre-emptive oral paracetamol administration is associated with significant analgesic benefits in patients undergoing laparoscopic bariatric procedures.

Keywords: Pre-emptive analgesia, Oral paracetamol, Bariatric surgery.

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1. Introduction

Morbid obesity constitutes a major public health problem in Egypt as it affects about 40% of the adult Egyptian population [1]. Currently, bariatric surgery is the most effective management option for such cases, as it offers better weight changes and comorbidity improvement compared to other options like lifestyle changes and medications [2, 3]. Nowadays, laparoscopy has become the standard approach for several bariatric procedures. Despite its minimally invasive nature compared to the open approach, many patients report moderate to severe postoperative pain, which could have detrimental effects on patient recovery [4, 5]. Pain after such procedures has three main components: parietal (from the abdominal wall ports), visceral (from intraperitoneal dissection), and shoulder tip pain [6, 7]. Opioid analgesics are effective options for maintaining perioperative analgesia during bariatric procedures. However, it has some undesired adverse events like hypotension, respiratory depression, somnolence, and gastrointestinal upset [8]. These adverse events will negatively affect patient recovery, especially since morbid obesity is associated with respiratory morbidity like obstructive sleep apnea and hypoventilation syndromes [9]. Pre-emptive analgesia has been described as a promising mode of analgesia that entails the administration of the pharmacological agent (or other pain management technique like regional blocks) prior to tissue injury. That is supposed to decrease central and peripheral sensitization, resulting in better analgesia compared to post-injury analgesic administration [10-12]. Paracetamol (acetaminophen) is a widely used analgesic that is used to maintain analgesia after different surgical procedures [13]. Its administration led to a significant reduction in pain intensity and opioid requirement in obese patients with obesity-related respiratory complications [14]. Although the administration of IV paracetamol has been widely studied as a pre-emptive analgesic in variable operations, including open and laparoscopic procedures [14], its pre-emptive oral

administration is understudied, especially in the bariatric population. That motivated us to cover that deficient research point in the current study that intended to elucidate if pre-emptive oral paracetamol has an opioid-sparing effect in patients undergoing laparoscopic bariatric surgery.

2. Patients and methods

This randomized prospective trial was conducted over a two-year period at "Gastrointestinal Surgical Center" (GISC) from January 2021 to December 2022. We designed our research for subjects aged between 18 and 50 years whose body mass index (BMI) ranged between 35 and 50 kg/m2 and scheduled for laparoscopic bariatric surgery. Patient enrolment did not start until we obtained ethical approval from "Mansoura University Institutional Review Board" (IRB code:MD.20.04.309). The preoperative assessment was done for all cases according to our center's protocol. That assessment included history taking (focusing on obesity-associated comorbidities), clinical examination (focusing on BMI), routine laboratory investigations, and cardiopulmonary assessment (including electrocardiogram, echocardiography, and pulmonary function tests if required). The physical status of the cases was classified according to the "American Society of Anesthesiologists" (ASA) [15]. Patients with class IV or more were excluded. Other exclusion criteria included allergy to the study medications, liver cirrhosis, patient refusal, need for conversion to the open approach, and the need for reoperation within 48 hours after the primary bariatric procedure. Seventy patients met our inclusion criteria, and their approval to participate in our study was documented in a written informed consent explaining the aim of the research, the benefits, and the possible disadvantages of each approach. Using the "closed envelop method," they were randomly assigned into two groups; Group I (n = 35) included cases who received pre-emptive paracetamol one hours prior to the laparoscopic procedure, and Group II (n = 35) included cases who received placebo at the same time. On the night before the operation, we instructed the cases on how to express their pain via the "visual analog scale" (VAS) [16]. The study was blinded in nature as the patients themselves, the attending anaesthesiologist, the operating surgeons, the staff nurse, and the resident physician responsible for data collection were blinded to group allocation. At the operative theatre, an IV line was secured for all cases, and standard hemodynamic monitoring was established. All patients were premedicated by IV dexamethasone (8 mg) and metoclopramide (10 mg). IV propofol (2.5 mg/kg) and fentanyl (1 mcg/kg) were used to induce general anesthesia, while IV atracurium (0.5 mg/kg) was commenced to facilitate tracheal intubation. IV ketorolac 15 mg was given after induction,ketamine at dose 0.25mg/kg, and magnesium sulfate was infused in 50 ml saline (15 mg/kg/hour). The anesthesia was maintained by isoflurane inhalation delivered through mechanical ventilation that was adjusted at a 6 ml/kg tidal volume and 1:2 IE ratio, and its rate was adjusted to keep end-tidal CO2 around 35 mmHg. Incremental doses of atracurium (0.15 mg/kg) were administered when required. During the laparoscopic procedure, heart rate (HR) and mean arterial pressure (MAP) were recorded every 15 minutes till the procedure ended. The anesthesia was reversed with IV atropine (0.25 mg/kg) and neostigmine (0.04 mg/kg). Both operative time and intraoperative isoflurane consumption were recorded. The latter was estimated using the equation proposed by Biro [17]. After extubation, the patients were transferred to PACU, where hemodynamic parameters and the initial VAS reading were recorded. After meeting the discharge criteria, the cases were transferred to the surgical ward. There, VAS was , at 0, 15 min, 30 min, 45 min, ,then 2,6,12 and 24 hours, whereas hemodynamic parameters were recorded every two hours during the first 12 hours and then every four hours till the end of the first postoperative day. IV paracetamol (1 g/six hours) was commenced for all cases for postoperative analgesia, and incremental doses of pethidine (0.5 – 2 mg/kg) were given if the patient reported breakthrough pain (VAS > 4). The time elapsed to the first call for opioid analgesia was recorded in both groups. We encouraged early mobilization in all cases, and any postoperative adverse events were recorded. All patients were discharged 24 hours after the procedure. The 24-hour opioid intake, VAS, time to initial rescue analgesia, changes in perioperative hemodynamic parameters, and the frequency of complications were our main study outcomes (Table 2).

2.1. Sample size calculation

Based on a prior pilot study with five participants receiving a placebo, the mean ± SD of total opioid analgesic consumption during the initial 24-hour period was 139.6 ± 40.5 mg. Using the two-tailed student T-test and assuming α error = 0.05 and β error = 0.2 (power = 0.8), each group needed 31 individuals to detect a 30-mg difference between groups, which is considered the least clinically significant effect. To allow subject dropouts, 35 subjects were assigned to each group.

2.2. Statistical analysis

We performed our statistical analysis using the SPSS software (version 26.0 for MacOS). We used either of the following tests to compare our two groups: the Chi-square (for categories), Mann-Whitney (for skewed quantitative data), or Student-t tests (for non-skewed quantitative data). The obtained p-values were considered significant if their values were less than 0.05.

3. Results and Discussion

Starting with baseline demographic data of the included subjects, the mean age of our participants was 42.51 years in Group I and 40.09 years in Group II. Women represented 71.4% of cases in Group I and 82.9% of cases in Group II, with higher prevalence compared to men in both study groups. Baseline BMI had average values of 40.6 and 40.14 kg/m2 in our two groups, respectively. The previous parameters and preoperative physical status, measured by ASA, in the two groups, did not express remarkable differences. As shown in Table 1, the duration of anesthesia and the laparoscopic procedure were also comparable between the study groups (p = 0.331 and 0.467, respectively). Intraoperative isoflurane consumption had a mean value of 57.29 ml in Group I and 56.57 ml in Group II, with no crucial difference in the statistical analysis. This is the first study to evaluate the beneficial effects of pre-emptive oral paracetamol on perioperative analgesic outcomes in bariatric surgery patients. That is considered a great advantage in favor of our research.

Table 1: Baseline parameters, operative and anesthetic durations, in addition to isoflurane consumption in the study groups.

Variables		Group I (Paracetamol Group) (n= 35)	Group II (Placebo Group) (n= 35)	P value
Age (years)		42.51 ± 9.04	40.09 ± 8.93	0.262
Sex	**Male**	10(28.6%)	6(17.1%)	0.255
	Female	25(71.4%)	2 9(82.9%)	
BMI (Kg/m^2)		40.60 ± 4.38	40.14 ± 3.26	0.622
ASA	**ASA II**	17 (48.57%)	20 (57.14%)	0 .472
	ASA III	18 (51.43%)	15 (42.86%)	
Operative time (min)		99.43 ± 9.06	98 ± 7.19	0.467
Duration of anesthesia (min)		110 ± 9.70	108 ± 7.19	0.331
Intraoperative isoflurane consumption (ml)		57.29 ± 7.51	56.57 ± 7.35	0.689

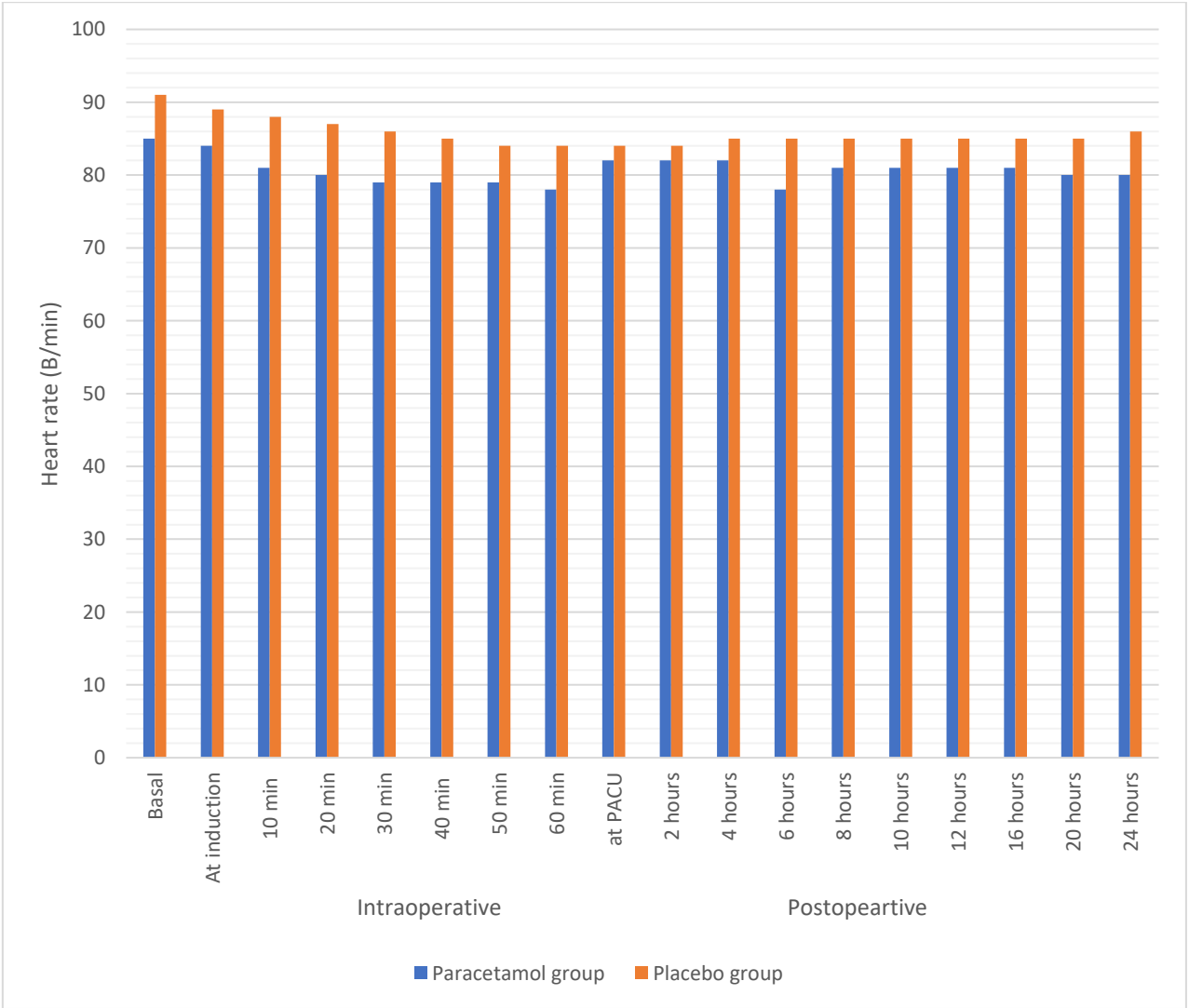

Figure 1: Baseline, intraoperative, and postoperative HR measurements.

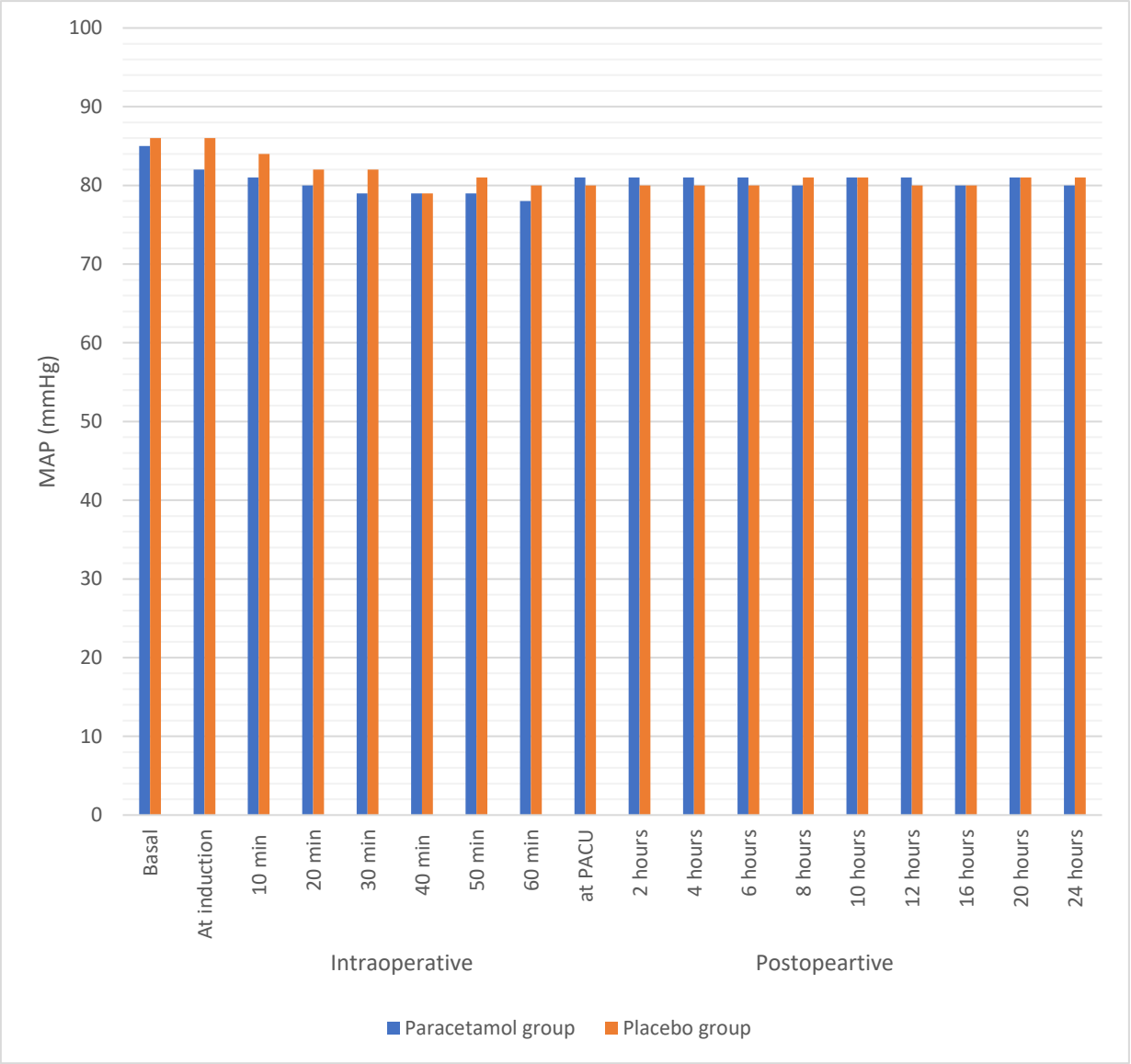

Figure 2: Baseline, intraoperative, and postoperative MAP measurements.

Table 2: Changes in VAS.

VAS	Group I (Paracetamol Group) (n= 35)	Group II (Placebo Group) (n= 35)	P value
PACU	2 (2 - 4)	3 (3 – 4)	**<0.001 ***
15 minutes	3 (2 – 5)	3 (3 – 6)	**<0.001 ***
30 minutes	3 (2 – 5)	4 (3 – 6)	**<0.001 ***
45 minutes	3 (2 – 5)	4 (3 – 5)	**0.008***
2 hours	3 (2 – 5)	3 (3 – 5)	0.305
6 hours	3 (3 – 5)	3 (3 – 5)	0.636
12 hours	3 (3 – 4)	3 (3 – 5)	0.453
24 hours	3 (3 – 4)	3 (3 – 5)	0.300

Table 3: Analgesia-related data

	Group I (Paracetamol Group) (n= 35)	Group II (Placebo Group) (n= 35)	P value
Time of first analgesic recall (min)	45 (15 – 120)	30 (15 – 60)	**< 0.001***
Total postoperative opioid consumption (mg)	40 (0 – 120)	80 (0 – 120)	**0.001***

Table 4: Postoperative complications

Side effects	Group A (Paracetamol Group) (n= 35)	Group B (Placebo Group) (n= 35)	P value
Nausea	8 (22.9%)	5 (14.3%)	0.356
Vomiting	6 (17.1%)	5 (14.3%)	0.743

Another advantage that should be considered is the lack of notable statistical differences between our groups regarding all baseline and preoperative parameters. Along with ensuring our efficient randomization technique, that should decrease the risk of bias, which may jeopardize our findings. We intended to administer paracetamol one hour before the operation, as the time till reaching maximum concentration when administered through the oral route is 120 minutes, as reported in previous studies [18, 19]. Singla and his associates reported that IV administration of the same medication is associated with a faster onset of action and higher plasma concentration [20]. Nonetheless, it is associated with more healthcare expenditure (48 $ for IV 1 gm vs. 0.02 $ for the same oral dose [21]. Thus, oral administration will be associated with less expenditure, which is of great benefit. Our results showed no notable differences in perioperative hemodynamic parameters between the two groups, and that could reflect proper analgesia provided in each group either intra or postoperatively. Our study revealed that pre-emptive oral paracetamol led to a significant decline in pain intensity for the initial 45 minutes following the surgical procedure. That could be explained by the central analgesic effects of paracetamol, which are mediated through activating descending serotonin pathways. Other analgesic mechanisms include inhibition of prostaglandin synthesis and activation of cannabinoid receptors [22]. Saha et al. reported similar effects when oral paracetamol (1 gm) was administered before laparoscopic cholecystectomy, as the measured pain scores significantly decreased after one, six, 12, and 24 hours following the laparoscopic procedure ($p = 0.027$) [23]. Other studies reported similar better analgesic outcomes with pre-emptive IV paracetamol) [24, 25].

In contrast to the previous findings, Turner et al. found no significant analgesic benefit when they administered 1 gm IV paracetamol prior to laparoscopic repair of the pelvic floor [21]. The authors explained their findings by the minimally invasive nature of urogynecological procedures that result in perioperative pain not high enough to express the clinical benefit of pre-emptive paracetamol. Our findings revealed that pre-emptive oral paracetamol led to a significant reduction in postoperative opioid needs. That should highlight the opioid-sparing effect of pre-emptive paracetamol, which is of great benefit in the obese population who have a potential risk for respiratory adverse events with opioid administration [26, 27]. Moreover, the administration of opioid analgesics in obese individuals may lead to cognitive impairment and gastrointestinal adverse events that may hinder fast postoperative recovery [28, 29]. Decreasing the need for opioids induced by pre-emptive paracetamol is expected to decrease the incidence of previous opioid-related adverse events. Saha and his colleagues reported similar findings as post-laparoscopic cholecystectomy opioid consumption was 126.8 ± 14.4 mg in the pre-emptive paracetamol group, which was higher than the placebo group (139.6 ± 9.5 mg) ($p = 0.012$) [23]. Other two studies reported similar opioid-sparing outcomes when pre-emptive IV paracetamol was given [25, 30]. Our study findings showed a significantly prolonged duration to the first rescue analgesic when pre-emptive paracetamol was administered. These findings are in accordance with previous studies which showed comparable outcomes with pre-emptive oral and IV paracetamol [23-25]. We did not note any notable differences in postoperative adverse events (nausea and vomiting) between the two groups. It is documented that paracetamol has a safe gastrointestinal profile with no ulcerogenic potential, like "non-steroidal anti-inflammatory drugs" (NSAIDs) [31, 32]. That is why we did not combine it with oral NSAID in the current study, especially since the patients were already having gastric surgeries. Arslan et al., on the other hand, reported that pre-emptive paracetamol led to a significant reduction in postoperative gastrointestinal adverse events [24]. Our study has some limitations; first of all, we included a relatively small sample size that was collected from a single surgical institution. Also, we should have combined paracetamol with oral NSAID, aiming to

increase the efficacy of analgesia. The previous drawbacks should be well addressed in the upcoming studies. All of the recorded baseline, intraoperative, and postoperative HR and MAP values showed no noteworthy differences when comparing our two groups (Figures 1 & 2). As explained in Table 3, pre-emptive oral paracetamol administration led to a significant decline in pain intensity during the initial 45 minutes following the operation, compared to the placebo group. Subsequent pain scores did not reveal any notable statistical differences. Pre-emptive oral paracetamol had additional benefits manifested in the prolongation of the first call for rescue analgesia and a decline in postoperative opioid consumption. The former parameter ranged between 15 and 120 minutes in Group I (median = 45) compared to a range between 15 and 60 minutes in Group II (median = 30). The latter had median values of 40 and 80 mg in the study groups, respectively (Table 3). The incidence of postoperative adverse events was comparable between the two groups (Table 4). Mobilization of all patients was done within three hours after the operation, and all patients were discharged from the hospital 24 hours after the operation as no patients had major postoperative adverse events, and they were able to take oral fluids before discharge (not shown in the tables).

4. Conclusion

Pre-emptive oral paracetamol given two hours before laparoscopic bariatric surgery is linked to a notable reduction in postoperative opioid consumption, a prolonging of the time to the first rescue analgesic, and a considerable lowering in postoperative pain scores.

Conflicts of interest

Nil.

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