

## ORIGINAL RESEARCH

## PAIN MANAGEMENT

# Role of vitamin C in multimodal analgesia for sleeve gastrectomy: a prospective randomized controlled trial

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## Abstract

**Background & Objective:** The laparoscopic sleeve gastrectomy is a popular intervention in morbidly obese patient. Postoperative pain relief is a major challenging issue in this procedure with known adverse effects on the respiratory excursion and the ability to cough by the patient. Various analgesic protocols have been tried to conquer this pain. Vitamin C is a micronutrient, water soluble vitamin with antioxidant and antinociceptive actions. We assessed the effect of vitamin C when used as a component of the multimodal analgesic technique in this cohort of the patients.

**Methodology:** After obtaining the ethical committee approval and trial registration, 50 patients scheduled for laparoscopic sleeve gastrectomy were enrolled in this study. The patients were randomly divided into two equal groups according to the study protocol. Group C received vitamin C 500 mg every 8 h for 5 days perioperatively, while Group N received placebo in the same fashion. The surgery was performed under routine general anesthesia. We monitored hemodynamic, VAS, rescue analgesia profile, and gastrointestinal side effects in the immediately after operation, and then at 1, 2, 4, 8, 12, and at 24 h postoperatively. The postoperative morphine consumption was noted as a primary objective of the study. Independent sample T test, Mann-Whitney test, chi square test or Kruskal Wallis test were utilized to detect statistical differences between the studied groups.  $P < 0.05$  was considered significant.

**Results:** Postoperative morphine consumption was lower in Group C than in Group N ( $16.36 \pm 2.37$  vs.  $20 \pm 4.13$  mg,  $P = 0.001$ ). The frequency of morphine was significantly lower in Group C than in Group N ( $P = 0.009$ ). VAS was lower in Group C than Group N at 4, 8, and 12 h postoperatively ( $P = 0.02, 0.001, 0.001$ ), while other parameters were comparable.

**Abbreviation:** CBC: complete blood count; IRB: Institutional Research Board; LFTs: liver function tests; LSG: laparoscopic sleeve gastrectomy; MABP: mean arterial blood pressure; NMDA: N-methyl D-aspartate; OSAS: obstructive sleep apnea syndrome; PACTR: Pan African Clinical Trial Registry; PEEP: positive end expiratory pressure.; PFT: pulmonary function tests; RFTs: renal function tests; TFTs: thyroid function test; TOF: train of four; VAS: visual analogue score.

**Preregistration:** Institutional Research Board, Mansoura Faculty of Medicine (IRB # R.20.02.738, Feb 15-2020). Pan African clinical trial registry (PACTR- 202003565796463, date of registration: March 02-2020).

**Conclusion:** Vitamin C via its antioxidant, antinociceptive properties and NMDA-receptor antagonist action can be used as a part of multimodal analgesic techniques. Vitamin C acts as co-analgesic, improves postoperative pain profile, and reduces the needs for other analgesic modalities.

**Key words:** Vitamin C; Analgesia; VAS; Pain; Sleeve Gastrectomy

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## 1. Introduction

Anesthesia and analgesia for morbidly obese patients is a real challenge. Beside the co-morbidities, the change in the pharmacokinetics and pharmacodynamics makes opioid use in large doses hazardous. The multimodal analgesia has improved efficacy and safety, and reduced rescue opioid consumption in these patients. Vitamin C is a micronutrient, water soluble vitamin, and has antioxidant as well as antinociceptive properties. Many studies have described its use in chronic pain due to its action on N-methyl D-aspartate receptors. We hypothesized that it would play an effective role in multimodal analgesia technique for patients undergoing laparoscopic sleeve gastrectomy without considerable side effects.

Obesity is a rapidly growing health problem all over the world and has a negative impact on the quality of lifestyle and more over on the survival.<sup>1</sup> Laparoscopic sleeve gastrectomy (LSG) has become one of the most performed bariatric surgical procedures over the last few years.<sup>2</sup> It is an easy, quick, and safe procedure, offering patients considerable weight loss.<sup>3</sup>

To alleviate pain response during the laparoscopic surgeries, a wide variety of drugs and techniques are being used both during the whole perioperative period. Many studies documented that preemptive analgesia caused attenuation of pain signals entering spinal cord, which is much more effective than controlling pain after signal input.<sup>4</sup>

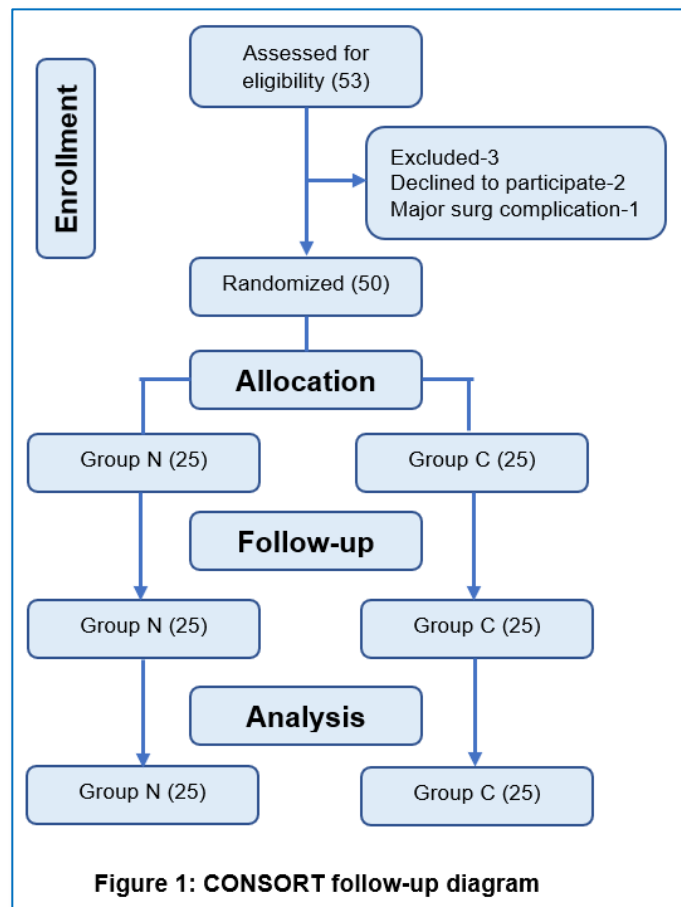
Obese patients are particularly having a higher sensitivity to the sedative and respiratory depressant effects of long-acting opioids. Obstructive sleep apnea syndrome (OSAS) is a common co-morbidity in obese patients. Such kind of patients are prone to airway obstruction, hypoventilation and oxygen desaturation in the postoperative period, especially if opioids and sedatives have been given.<sup>5</sup> In this background, multi-modal analgesia has been advised for bariatric surgery to reduce the opioid consumption and the associated hazards.<sup>6</sup>

Vit C is a water-soluble vitamin which exerts its anti-nociceptive properties through its antioxidant action by neutralizing the reactive oxygen species formed during the stress of surgery. In addition, it also has a role in modulating the sensitization of

pain through its action on NMDA receptors. Therefore, it might be useful in reduction of pain sensation without side effects.<sup>7-9</sup> We assessed the effect of vitamin C when used as a component of the multimodal analgesic technique in this cohort of the patients.

## 2. Methodology

The study was approved by the Committee of the Institutional Research Board, Mansoura Faculty of Medicine (IRB # R.20.02.738, Feb 15-2020). Informed consent was obtained from all participants in the trial. The trial was registered in the Pan African Clinical Trial Registry (vide No. PACTR- 202003565796463; dated: March 02-2020). Fifty adult patients of both genders, ASA PS-I and II, 18-45 y old, scheduled for laparoscopic sleeve gastrectomy in Mansoura gastro-enterology surgical center were enrolled in this study in accordance to CONSORT guidelines (Figure 1). While, exclusion criteria were patient refusal, addiction, allergy to vitamin



C, cardiopulmonary disorders, altered liver, kidney or thyroid function tests, psychological troubles, or complicated procedure. Random number generator with closed envelope technique randomized patients into two groups based on taking vitamin C: 25 in Group C, 25 for placebo group (Group N).

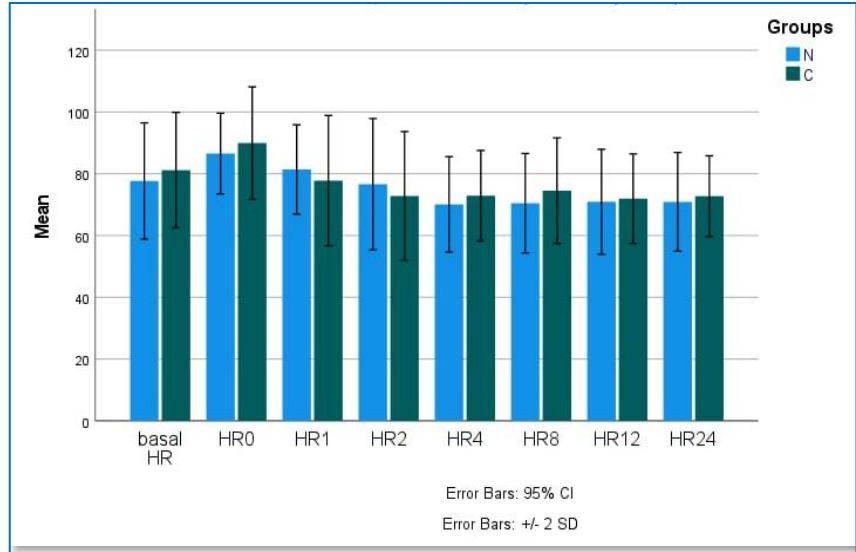
Group C patients took 500 mg vitamin C as an oral capsule every 8 h, for 5 days (4 days preoperative, and the operative day). While, Group N patients took placebo with identical regimen.

Assessment of anesthetic fitness, and explanation of the procedure was done for all patients during their visit to pre-anesthesia clinic. Preoperative assessment included medical and surgical history, airway assessment, body mass index, pulmonary function test (PFT), ECG, echocardiography, complete blood count (CBC), liver function tests (LFTs), renal function tests (RFTs), thyroid function test (TFT), and coagulation profile.

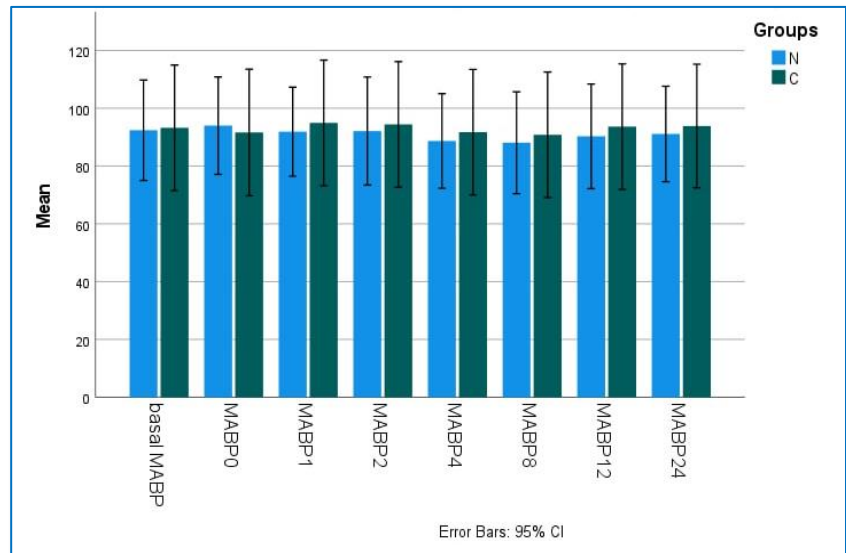
The standard general anesthesia protocol was identical in both groups and started in the preoperative suite under monitoring: based on, preoperative pantoprazole (Zurcal®, AUG Pharma™, Spain) 40 mg IV, dexamethasone (Dexamethasone, Sigmatec™, Egypt) 8 mg IV and midazolam (Midathetic®, Amoun™ Pharmaceuticals) 3 mg IV. Ringer acetate infusion was started at a rate of 4 ml/kg/h and continued as a maintenance fluid till the end of the surgery. In the operating room, the patients were connected to the basic monitors (ECG, NIBP, SpO<sub>2</sub>), anesthesia was induced using propofol (Diprivan®, Fresenius KABI™) 1-2 mg/kg, fentanyl (fentanyl Hameln®, Hameln Pharmaceuticals™, Germany) 1.5 µg/kg, atracurium 0.6 mg/kg (Atrabesylate®, EGYPT Pharm™, Egypt). Endotracheal intubation was done by a proper sized armored endotracheal tube and the tube fixed in place after confirmation of correct positioning by capnography and lung auscultation. Patients were ventilated using (GE Datex-Ohmeda

Aisys®, USA) closed circuit ventilator, with volume-controlled ventilation mode; initial settings were tidal volume 6–8 ml/kg, RR 12–15 pm, PEEP 5–8 cmH<sub>2</sub>O, FiO<sub>2</sub> 0.4 to keep EtCO<sub>2</sub> around (35 ± 2 mmHg). Inj. paracetamol 1gm was infused as a part of multimodal analgesia technique. Before starting of surgery, two peripheral intravenous lines, and a suitable sized urinary catheter were inserted.

Sevoflurane 1.5–2% in 40% oxygen-air mixture was used in inhalational maintenance of anesthesia. Increments of atracurium 0.1 mg/kg were given as needed, by train of four (TOF) monitoring to keep no more than two twitches present (> 80% block).



**Figure 2: Comparative perioperative heart rate (HR) at different times**



**Figure 3: Comparative perioperative mean arterial blood pressure (MABP) at different times**

Abdominal insufflation pressure was kept within 13–15 mmHg.

After completion of the surgery, the surgeon did gentle abdominal pressure to allow evacuation of insufflating gas while the patient was in supine position. Trocars sites were

infiltrated by 10 ml lidocaine 2% for relief pain at the end of surgery. Muscle relaxation was reversed using neostigmine 0.05 mg/kg plus atropine 0.02 mg/kg, and awake extubation was performed after fulfilment of extubation criteria. For postoperative analgesia paracetamol 1 gm every 6 h, and rescue opioids (morphine 0.05–0.10 mg/kg) were used if VAS was more than 4. Patients were left in post-anesthesia care unite for 2 h before transfer to the ward.

Collected data included total rescue morphine consumption within the first postoperative 24 h as a primary objective of the study. Number of rescue analgesia requests within the first postoperative 24 h and time to first request were noted. Heart rate (HR), mean arterial blood pressure (MAP), VAS scores were noted immediately after operation, and at 1, 2, 4, 8, 12, and at 24 h postoperatively.

Also, gastrointestinal irritation symptoms (nausea, vomiting) within the first postoperative 24 h were documented. Data collection was done by trained nursing staff either in PACU or in the patient’s ward.

**Statistical analysis**

For sample size calculation, using a pilot study on 5 cases scheduled for laparoscopic sleeve gastrectomy in each group, and considering total rescue morphine consumption within the first postoperative 24 h as a primary objective of the study, the mean and slandered deviation in Group C was  $18.4 \pm 2.40$  and in Group N was  $21.6 \pm 4.16$ , allowing for alpha error 0.05 and beta

error +0.1 (power = 90%), 24 cases were needed in each group. Allowing 5% drop error, 25 cases were analyzed in each group.

Cases in the pilot study were not included in the study groups. Perioperative data were tabulated and analyzed using IBM SPSS software version 22. Continuous data were presented as mean  $\pm$  SD or median (IQR) according to the normality of distribution. Nominal and categorical data are presented as numbers and percentages. Independent sample T test, Mann-Whitney test, chi square test or Kruskal Wallis test were utilized to detect statistical differences between the studied groups. A  $P < 0.05$  was considered significant.

**Table 1: Demographic data and Postoperative adverse effects in 24 h in the studied groups.**

Variable	Group N (n = 25)	Group C (n = 25)	P value
Age (y)	34.32 $\pm$ 7.55	36.76 $\pm$ 7.32	0.25
BMI (kg/m <sup>2</sup> )	57.16 $\pm$ 7.26	55.96 $\pm$ 8.21	0.58
PONV occurrence	9 (36%)	7 (28%)	0.54

Data are presented as mean  $\pm$  SD, numbers, and percent %; BMI: Body Mass Index, Kg: kilogram, m: meter, PONV: postoperative nausea and vomiting; \*Significant P value when  $< 0.05$ .

**Table 2: Profile of rescue analgesia, Data are expressed as mean  $\pm$  SD.**

Variable	Group N (n = 25)	Group C (n = 25)	P value
Time to first morphine request (min)	6.96 $\pm$ 5.38	6.80 $\pm$ 5.75	0.90
Number of morphine intake within 24 h.	4 (2–6)	3 (2–4)	0.009*
Total morphine consumption within 24 h.	20 $\pm$ 4.13	16.36 $\pm$ 2.37	0.001*

Min: minutes, H.: hours; \*  $P < 0.05$  considered as significant.

**Table 3: Comparative visual analogue scale scores (VAS) in the groups Data are presented as median and range.**

Time to measure	VAS		P value
	Group N (n = 25)	Group C (n = 25)	
Postop	6 (4–8)	6 (4–8)	0.85
1 h	5 (3–6)	4 (3–6)	0.09
2 h	4 (3–6)	4 (3–5)	0.49
4 h	4 (2–5)	3 (2–4)	0.020*
8 h	3 (2–4)	2 (1–3)	0.001*
12 h	2 (1–4)	1 (0–3)	0.001*
24 h	0 (0–1)	0 (0–1)	0.25

VAS: visual analogue score; \*  $P < 0.05$  considered as significant.



### 3. Results

53 patients were recruited for this prospective randomized controlled study, 3 cases were excluded while 50 patients were equally divided between both groups and completed the study protocol, Figure 1. As shown in Table 1, no statistically significant differences were detected between both of the study groups regarding patient demographics, and postoperative gastrointestinal symptoms, e.g., nausea and vomiting. Basal and postoperative hemodynamic data are expressed in Figure 2 for HR, and in Figure 3 for MABP, without any statistical significance between the two study groups.

The profile of rescue analgesia, and total morphine consumption was significantly lower in Group C than Group N ( $P = 0.001$ ) as shown in Table 2. Also, the frequency of morphine used was significantly lower in Group C than in Group N ( $P = 0.009$ ), while the time to first requirement of morphine intake was comparable in both groups.

Table 3 shows the comparative VAS scores in the study groups at baseline and at 1, 2, 4, 8, 12, and 24 h after completion of surgery. VAS scores were comparable in both study groups at 0, 1, 2 and 24 h after surgery ( $P = 0.85, 0.09, 0.49, 0.25$  respectively); however, at 4, 8 and 12 h, VAS was statistically lower in the Group C than in the Group N ( $P = 0.02, 0.001, 0.001$  respectively).

### 4. Discussion

This study investigated the effect of perioperative use of vitamin C on postoperative pain profile and rescue analgesia consumption in obese patients undergoing laparoscopic sleeve gastrectomy.

Postsurgical pain is an agonizing problem, while the laparoscopic procedure is less painful, but it has different components including; somatic, visceral and shoulder pain.<sup>10</sup> Strategies and protocols applied to improve pain profile after laparoscopic surgeries included the use of multimodal analgesia, regional blocks, and intraperitoneal instillation of local anesthetics. Also, to avoid shoulder pain, low insufflating pressure, complete evacuation of the abdomen, pulmonary recruitment maneuver, extended hyperventilation and gasless surgeries have been advised to avoid the peritoneal and diaphragmatic irritation by CO<sub>2</sub>.<sup>11,12</sup> Obesity is a second challenge, as excessive postoperative opioids consumption will affect the ventilation in already compromised patients. So, the reduction of the postoperative use of opioids analgesia while maintaining adequate analgesia level is a great task. Vitamin C (ascorbic acid) is a water-soluble vitamin, readily available, cheap, easy to use and with minimal side effects at the prescribed dose.<sup>8</sup>

Our results show that postoperative analgesic profile was better in Group C, lower total morphine consumption, and lower VAS scores at 4, and 12 hours postoperatively, with comparable results regarding hemodynamics, and postoperative gastrointestinal irritation symptoms and complications.

Vitamin C is one of the most powerful reductant agents with its antioxidant, free radical scavenger, neuroprotective, and neuromodulation effects.<sup>13</sup> It was shown to modulate the neurotransmission of dopamine and glutamate through the redox changes on the N-methyl-D-aspartate (NMDA) receptor. Vitamin C is also important in the biosynthesis of neurotransmitters. It acts as a cofactor for dopamine  $\beta$ -hydroxylase, which is the rate-limiting step in the formation of norepinephrine and is involved in cholinergic and GABAergic transmission. These neurotransmitters are well known to be the main components of the inhibitory pain pathway.<sup>14</sup> In addition, it has been shown to reduce acute pain and the prevalence of complex regional pain syndromes with its antinociceptive effect.<sup>15</sup> Also, it plays an important role in collagen synthesis, which is important for healing of injured skin and scar tissue, tendons, ligaments, and blood vessels.<sup>16</sup>

Hung KC et al., in a recent meta-analysis postulated that vitamin C exerts significant reductions in pain scores (VAS) and opioid use and requirement up to 24 h postoperatively respectively, suggesting the effectiveness of perioperative vitamin C use.<sup>8</sup> Other investigators concluded similar results, while using higher intravenous dose in laparoscopic colectomy, and cholecystectomy patients.<sup>14,17</sup>

Some other trials supported the efficacy of vitamin C in open surgeries and trauma patients.<sup>13, 18, 19</sup> Jain SK. Et al. suggested that vitamin C limits the soft tissue injury by reducing the progression of vascular permeability leading to reduction in the leakage of proteins and fluids in the interstitial spaces and also by reducing the lipid peroxidation.<sup>16</sup> This may potentially reduce the post-operative swelling, edema and pain. Vitamin C promotes healing of soft tissue and bone by synthesis of intercellular substances like collagen, bone matrix and intercellular cement of the capillary endothelium.<sup>20</sup>

Moreover, vitamin C has promising results in chronic pain management, complex regional pain syndrome, cancer pain, and improving outcome in trauma and major orthopedic surgeries.<sup>16,21-25</sup>

Hemodynamic parameter and gastrointestinal irritation (nausea and vomiting) symptoms were comparable in both groups, no unanticipated complications could be detected regarding the study protocol.

## 5. Limitations

Our study had some limitations; we did not measure the serum level of vitamin C, and fixed only a limited time for postoperative patient observation (only for 24 h). Long term observation may reflect a more obvious results regarding pain and surgical healing of the tissue. Comparing other routes of vitamin C administration as intravenous route may be helpful regarding bioavailability and serum concentration during the whole perioperative times.

## 6. Conclusion

Vitamin C is a water-soluble vitamin, has antioxidant and antinociceptive properties, plays a favorable role in multimodal analgesia techniques and reduces the needs of rescue analgesia in laparoscopic sleeve gastrectomy in morbidly obese patients.

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## 9. Conflict of interest

The authors disclose no conflict of interest.

## 10. Authors contribution

MA: Prepared study design, writing manuscript, submitting manuscript.

MA: Collecting data, did the statistics.

Mm: Collecting data, review the manuscript.

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