

# Effect of clonidine versus dexmedetomidine on pain control after laparoscopic gastric sleeve: A prospective, randomized, double-blinded study

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## ABSTRACT

**Background:** The use of opioids in surgeries for morbidly obese patients could cause respiratory depression. Therefore, alternative analgesics are needed to improve anesthetic management for obese patients. The objective of this study was to compare the effect of dexmedetomidine and clonidine on pain as well as analgesic consumption at 24 h postoperatively in patients undergoing laparoscopic gastric sleeve. The secondary objective was to compare patients' and surgeons' satisfaction. **Materials and Methods:** A total of 60 obese and morbidly obese patients scheduled to undergo laparoscopic gastric sleeve were randomly assigned into two groups. 10 min after induction of general anesthesia, one group received 0.8-1.2 µg/kg/30 min intravenous (IV) clonidine through 500 mL lactated Ringer's solution and placebo (normal saline solution) through syringe pump. The second group received IV dexmedetomidine through syringe pump at a rate 0.5-0.8 µg/kg/h and placebo through 500 mL lactated Ringer's solution. Data on pain, analgesic consumption, and return to normal activity in addition to patients' and surgeons' satisfaction were collected. **Results:** Both groups were similar with respect to demographic and intraoperative hemodynamic characteristics. Fentanyl consumption, surgery duration and hospital stay were similar for the two groups. Pain scores on walking were significantly lower in the clonidine group at 12 h postoperatively ( $P = 0.014$ ) compared with dexmedetomidine group. The number of patients who consumed pethidine was significantly lower in the clonidine group at 12 h postoperatively ( $P = 0.045$ ). **Conclusion:** This study concluded that clonidine and dexmedetomidine yielded similar outcomes with a difference in pain and analgesic consumption at 12 h postoperatively.

**Key words:** Analgesia, opioids, postoperative pain

## INTRODUCTION

The frequency of bariatric surgery has been increasing worldwide due to the escalating prevalence of obesity.<sup>[1]</sup> It has been challenging for anesthesiologists to define the most effective anesthetic management of morbidly obese patients. Anesthesiologists may encounter intraoperative hemodynamic and respiratory problems such as reduced functional residual capacity and hypoxemia.<sup>[2,3]</sup> In addition, morbidly obese patients are at a higher risk of developing

sleep apnea and reduction in tissue oxygenation, which in turn leads to insufficient postoperative ventilation.<sup>[4]</sup> Moreover, the use of opioids in surgeries for morbidly obese patients is controversial since they are known for having ventilatory depressing effects. Therefore, alternative analgesics are needed to improve anesthetic management for obese patients.<sup>[1]</sup>

For this reason, several studies were conducted to adopt an effective anesthetic management model in order to reduce opioid consumption.<sup>[5,6]</sup> The use of alpha-2 agonists, dexmedetomidine, and clonidine, have been studied as alternatives to opioids. These have been shown to decrease the consumption of anesthetics and analgesics intra- and postoperatively, while maintaining hemodynamic stability. They also have negligible respiratory depressing effects.<sup>[6,7]</sup> However, there is no agreement for the most effective agonist that produces desirable outcomes without side-effects.<sup>[6]</sup>

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## MATERIALS AND METHODS

Following the approval from the Institutional Review Board, written informed consent was obtained from patients whose ages ranged between 20 and 53 years scheduled to undergo laparoscopic gastric sleeve. Sixty obese and extremely obese patients (body mass index [BMI] >30 kg/m<sup>2</sup>) (ASA physical status II or III) were enrolled in this prospective, randomized, and double-blinded study conducted from January 2012 to January 2013. The BMI was calculated in kg/m<sup>2</sup> and categorized as overweight, obese, and extremely obese.<sup>[8,9]</sup> Exclusion criteria included: Patients with severe chronic obstructive pulmonary disease, uncontrolled hypertension, atrioventricular block, older than 60 years, and who refused to participate in the study.

The sealed envelope technique was used to randomly allocate patients into two groups with 30 patients each. At the operating room, Ringer's lactate infusion was started. 10 min after induction of general anesthesia, one group received intravenous (IV) clonidine (Catapres, Boehringer Ingelheim, Germany) 0.8-1.2 µg/kg/30 min through 500 mL lactated Ringer's solution and placebo (normal saline solution) through syringe pump. The second group received IV dexmedetomidine (Precedex, Hospira, Inc. Lake Forest, USA) through a syringe pump at a rate 0.5-0.8 µg/kg/h (supplied in 2 mL ampoules at a concentration 200 µg/2 mL that was diluted in 50 mL normal saline to obtain 4 µg/mL) and placebo through 500 mL lactated Ringer's solution, while monitoring hemodynamics. The lactated Ringer's solution was kept for 30 min, while the syringe pump was removed at the time of wound closure. All patients received 4 mg intraoperative Zofran (Ondansetron, Aguetant, France) and 50 mg Rantag (Julphar, UAE). Thirty minutes before the end of the surgery, patients were given 1.5-2 mg/kg IV Tramadol Hydrochloride (Tramal, Grunenthal, Germany) and 1 g Paracetamol (Panpharma, France).

Double-blinding was ensured by allowing an independent nurse to prepare the study drugs outside the operating room. The anesthesiologists, surgeons, anesthesiology residents who collected the data and patients were unaware of the groups.

### Protocol for general anesthesia

Induction of anesthesia was done using IV fentanyl (1 µg/kg), propofol (1.5-2 mg/kg), and midazolam (1-2 mg)

followed by endotracheal intubation facilitated by nimbex (0.15 mg). Anesthesia was maintained by sevoflurane (1-1.5%), fentanyl (0.5 µg/kg/h), nimbex (0.05 mg/kg/h), 60% nitrous oxide and 40% oxygen. Any hemodynamic change of 25% resulted in a gradual increase or decrease of the sevoflurane concentration. A decrease of more than 25% was considered hypotension and was managed using 6 mg IV ephedrine (Aguettant, France).

### Data collection

The intraoperative data included mean arterial pressure, heart rate (HR), and oxygen saturation those were observed before starting the operation (baseline), then pre and post-incision, and in the postanesthesia care unit (PACU).

The postoperative data were collected at predetermined time intervals (0, 6, 12 h, and days 1-5 postoperatively). The data included surgery duration, self-transportation to stretcher, postoperative nausea and vomiting (PONV), return to normal daily activity, pain scores in addition to analgesic consumption. Pain was measured using the visual analog scale (VAS) with a score of 0 denoting no pain and 10 maximum possible pain. Pain was assessed at rest and while walking. Patients were told that they will be contacted through phone calls after their hospital discharge on a daily basis and will be asked about their pain intensity and analgesic consumption. Patients were followed-up by anesthesiology resident for five postoperative days.

Patients' and surgeons' satisfaction were assessed using a scale rating from 1 to 3 (1-unsatisfied, 2-partially satisfied, and 3-satisfied). Surgeon's satisfaction was based on the overall intra- and post-operative status of the patient. The intraoperative criteria included patients' movement. The postoperative criteria included patient agitation and number of phone calls made by patients. Patient's satisfaction was assessed according to the patient's comfort and activity. Patient's comfort was determined by the following criteria: Feeling of pain, PONV, and negative or bad memory of the procedural experience. The patient's activity was based on the ability to sit, walk, move, and return to the usual daily activity.

### Postoperative pain management

Patients were given systematically 1 g Paracetamol every 6 h during their hospital stay. Patients with VAS score between 3 and 5 were given IV Tramadol Hydrochloride (Tramal, Grunenthal, Germany) 100 mg every 8 h. Patients with a VAS score >5 received IM 1 mg/kg Dolosal with a maximum dose of 100 mg (Pethidine Renaudin, Laboratoire Renaudin, France).

### Statistical analysis

Data were reported as mean standard deviation, or number of patients (percentage) *t*-test (two-tailed) and Chi-square test

were used to assess any significant difference between the two groups.  $P < 0.05$  was considered as significant. A sample size of 30 patients in each study group was sufficient to detect a 50% reduction in VAS scores at 24 h postoperatively.<sup>[10]</sup>

## RESULTS

The study began with 72 patients scheduled to undergo gastric sleeve. Twelve patients were excluded: Three patients had comorbidities (asthma, diabetes, and hypertension), one patient had coronary artery disease and atrioventricular block, five patients were older than 60 years and three refused to participate. Thus, 60 patients were eligible for the study. As a result, 30 patients were included in each group [Figure 1].

Both groups were similar with respect to age, height, weight and intraoperative hemodynamic characteristics [Table 1, Figures 2 and 3]. Fentanyl and ephedrine consumption, self-transportation to stretcher, surgery duration, hospital stay and number of patients who returned to daily activity (within the five follow-up days) were similar for the two groups. The incidence of PONV was similar in both groups. Moreover, there were no significant differences with respect to patients' satisfaction (93.3% vs. 86.7%) and surgeons' satisfaction (96.7% vs. 93.3%) between clonidine and dexmedetomidine groups, respectively [Table 2].

There was no significant difference in pain scores during the patients' stay at the PACU (0 h) and at 6 h postoperatively. The pain scores on walking were significantly lower in the clonidine group at 12 h postoperatively ( $P = 0.014$ ). Pain scores at 24 h were similar in both groups [Table 3].

There was no significant difference in the number of patients who consumed pethidine at the PACU and 6 h postoperatively. The number of patients who consumed pethidine was significantly lower in the clonidine group at 12 h postoperatively ( $P = 0.045$ ). The consumption of tramadol at 12 h postoperatively was comparable in the two groups. There was no significant difference in analgesic consumption at 24 h postoperatively [Table 3].

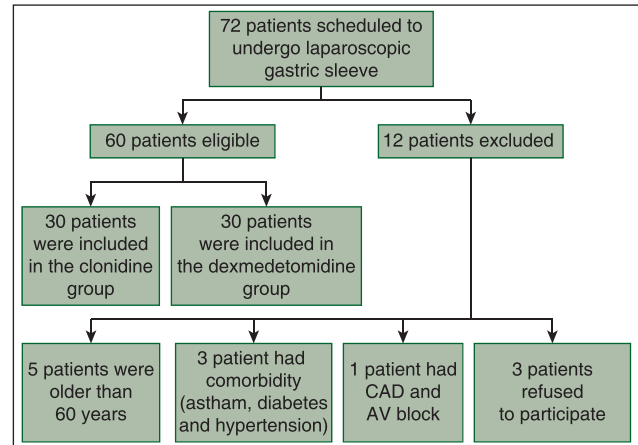
**Table 1: Patients' demographic characteristics**

Characteristics	Clonidine group (n = 30)	Dexmedetomidine group (n = 30)	P value
Gender (%)			
Male	7 (23.3)	13 (43.3)	0.100
Female	23 (76.7)	17 (56.7)	
Age (years)	32.13 (9.6)	31.21 (6.9)	0.672
Weight (kg)	126.85 (27.4)	125.31 (24.2)	0.821
Height (cm)	165.79 (9.0)	169.18 (8.8)	0.178
BMI (kg/m <sup>2</sup> )	46.31 (9.9)	43.52 (6.1)	0.222

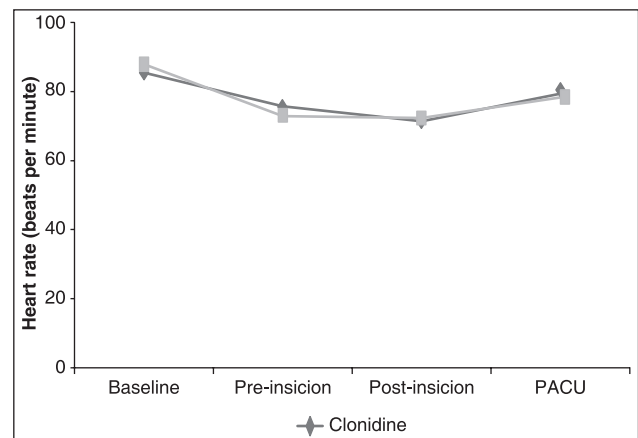
Data are presented as mean (standard deviation) or number of patients (%); BMI: Body mass index

## DISCUSSION

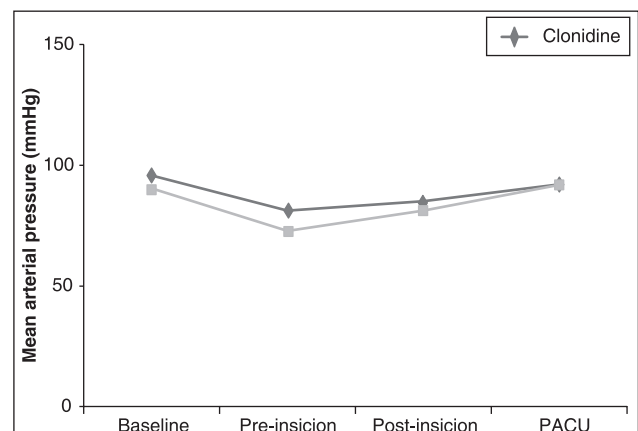
The results of the present study could be attributed to several factors. One of the factors might be the longer elimination half-life of clonidine.<sup>[7]</sup> Thus, it had prolonged the duration of postoperative analgesia and showed opioid-sparing effect.<sup>[11,12]</sup> Various studies revealed that the use



**Figure 1:** Flowchart illustrating the selection of patients



**Figure 2:** Average heart rate at different time intervals



**Figure 3:** Mean arterial pressure at different time intervals

**Table 2: Intra- and post-operative data**

Intra- and post-operative description	Clonidine group (n = 30)	Dexmedetomidine group (n = 30)	P value
Peroperative consumption			
Fentanyl (µg)	371.71 (73.9)	337.50 (85.3)	0.103
Ephedrine (%)	6 (20.0)	7 (23.3)	0.754
Duration of anesthesia (min)	182.30 (39.9)	171.50 (27.6)	0.241
Duration of surgery (min)	138.01 (38.1)	126.03 (24.6)	0.153
Self-transportation to stretcher (%)	26 (86.7)	25 (89.3)	0.760
Incidence of PONV (%)	9 (37.5)	13 (52.0)	0.308
Time of first (h)			
Urination	7.43 (4.7)	7.68 (7.9)	0.851
Defecation	58.30 (34.3)	52.38 (24.3)	0.489
Patients' satisfaction (%)			
Satisfied	28 (93.3)	26 (87.5)	0.389
Partially satisfied	2 (6.7)	4 (13.3)	
Surgeons' satisfaction (%)			
Satisfied	29 (96.7)	28 (93.3)	0.554
Partially satisfied	1 (3.3)	2 (6.7)	
Hospital stay (%)			
1 day	24 (80.0)	25 (83.3)	
2 days	6 (20.0)	5 (16.7)	0.739
Patients returned to daily activity within the five follow-up days (%)	21 (70.0)	19 (63.3)	0.584

Data are presented as mean (standard deviation) or number of patients (%); PONV: Postoperative nausea and vomiting

**Table 3: Average pain scores and analgesic consumption at different time intervals**

Pain and analgesics	Clonidine (%)	Dexmedetomidine (%)	P value
Average pain scores at			
0 h			
At rest	2.29 (2.1)	3.27 (2.1)	0.101
6 h			
At rest	2.09 (1.9)	3.38 (2.8)	0.091
On walking	3.03 (2.1)	3.87 (2.2)	0.133
12 h			
At rest	2.62 (1.7)	3.20 (1.8)	0.257
On walking	2.85 (1.9)	4.24 (1.9)	0.014
24 h			
At rest	2.56 (2.1)	2.83 (1.7)	0.591
On walking	2.96 (2.2)	3.93 (1.7)	0.070
Number of patients consuming analgesics at			
0 h			
Pethidine	1 (3.3)	3 (10.0)	0.301
6 h			
Pethidine	7 (23.3)	11 (36.7)	0.260
12 h			
Tramadol	1 (3.7)	1 (3.7)	1.000
Pethidine	5 (16.7)	12 (40.0)	0.045
24 h			
Tramadol	0 (0.0)	1 (3.3)	0.313
Pethidine	3 (10.0)	2 (6.7)	0.640

Data are presented as mean (standard deviation) or number of patients (%)

of IV clonidine had decreased postoperative morphine consumption.<sup>[11,13]</sup> This could be explained by the synergetic

analgesic action between opioids and alpha-2-adrenergic agonists.<sup>[14]</sup>

Another factor could be the analgesic effect resulting from systemic clonidine attributed to the association between clonidine and the alpha-2 receptors.<sup>[15]</sup> The alpha-2-adrenergic receptors are located on the afferent terminals of neurons situated in the superficial laminae of the spinal cord. They are also found in some brainstem nuclei such as the locus coeruleus (in the dorsal medulla).<sup>[16]</sup>

A third factor might be related to the dose of clonidine. Many studies were conducted to assess the effect of different doses of clonidine on postoperative opioid consumption.<sup>[17]</sup> De Kock *et al.* found that the intraoperative infusion of IV clonidine (loading dose 4 µg/kg/30 min then 2 µg/kg/h) decreased morphine consumption through patient-controlled analgesia during the first 12 h after abdominal surgery.<sup>[13]</sup> Another study by Bernard *et al.* showed that the postoperative administration of IV clonidine (loading dose 5 µg/kg for 30 min followed by 0.3 µg/kg/h) had reduced pain scores and morphine consumption within 12 h after spinal surgery.<sup>[11]</sup>

On the other hand, dexmedetomidine is a highly selective alpha-2 adrenergic receptor agonist with sedative, analgesic, anxiolytic and sympatholytic properties. Its elimination half-life is about 2 h.<sup>[1]</sup> However, its affinity to alpha-2 receptors is about eight times greater than clonidine.<sup>[10]</sup> Several studies on bariatric and nonbariatric surgeries showed that dexmedetomidine

reduced postoperative analgesic and opioid consumption and recommend its use.<sup>[18,19]</sup> Tufanogullari *et al.* concluded that the use of dexmedetomidine in laparoscopic bariatric surgery had reduced fentanyl consumption, antiemetic therapy and PACU stay. However, it failed to produce opioid sparing effect in the late postoperative period due to its short elimination time.<sup>[1]</sup>

Few studies had compared clonidine to dexmedetomidine.<sup>[20]</sup> A prospective observational study conducted by Panda *et al.* had compared clonidine, dexmedetomidine (1 µg/kg/10 min through infusion pump preinduction) and a control group. Both study groups had significantly reduced the intraoperative use of opioids, analgesics and thiopentone compared with the control group. They also showed that there was no significant difference between clonidine and dexmedetomidine groups with respect to opioid and anesthetic sparing effects intraoperatively. However, they did not assess the effect of both agonists postoperatively.<sup>[20]</sup>

Moreover, the sympatholytic effect of dexmedetomidine and clonidine reduces blood pressure and HR.<sup>[4,20]</sup> In this study, there was no significant difference in the number of patients who consumed ephedrine between the two groups; six versus seven patients in the clonidine and dexmedetomidine groups respectively. Hence, only these patients had reduced blood pressure implying that the dose of clonidine and dexmedetomidine did not cause severe hypotension. However, decreased blood pressure might also be caused by the reverse trendelenburg position.<sup>[21]</sup>

The design of intraoperative administration of the two agonists was based on recommendations from other studies and feasibility of the technique. The selection of dexmedetomidine dose was consistent with the recommended values ranging between 0.2 and 0.7 µg/kg/h to reduce the risk of cardiovascular adverse effects<sup>[1,4]</sup> Moreover, clonidine dose was chosen to be 0.8-1.2 µg/kg/30 min to avoid side effects.<sup>[20]</sup>

A limitation in the current study was the absence of a control group. This prevented us from assessing the difference in the effect produced by the presence or absence of clonidine and dexmedetomidine. However, the decision of not enrolling a control group was based on the fact that other studies had compared dexmedetomidine or clonidine with a control. They showed that dexmedetomidine or clonidine had resulted in reduced postoperative analgesic consumption in comparison to the control group.<sup>[1,4,6,13]</sup>

## CONCLUSION

This study concluded that 0.8-1.2 µg/kg/30 min clonidine and 0.5-0.8 µg/kg/h infusion of dexmedetomidine yielded

similar outcomes with a difference in pain and analgesic consumption at 12 h postoperatively. No cardiovascular complications occurred in this study. Nevertheless, the dose of dexmedetomidine used in the current study might not be enough to significantly decrease pain in the first 12 h postoperatively. Further studies are needed to assess the effectiveness of different doses of dexmedetomidine.

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