

## EFFECTS OF DEXMEDETOMIDINE IN MORBIDLY OBESE PATIENTS UNDERGOING LAPAROSCOPIC GASTRIC BYPASS

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### Abstract

**Background:** Obese patients may be sensitive to the respiratory depressant effect of opioid analgesics. Alternative methods for analgesia may be beneficial for management of bariatric surgery. We evaluated the effect of dexmedetomidine on anesthetic requirements during surgery, hemodynamic, recovery profile and morphine use in the postoperative period.

**Methods:** Eighty adult patients scheduled for elective laparoscopic Roux-en-Y gastric bypass surgery were randomly assigned to one of two study groups; Group D (40 patients) received dexmedetomidine (0.8- $\mu\text{g}/\text{kg}$  bolus, 0.4  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) and Group P (40 patients) received normal saline (placebo) in the same volume and rate. Intraoperative and postoperative mean blood pressure and heart rate were recorded. The total amount of intraoperative fentanyl and propofol required to maintain anesthesia were measured. Recovery profile, pain score and total amount of morphine used via patient controlled analgesia (PCA) were assessed.

**Results:** During surgery, dexmedetomidine decreased the total

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amount of intraoperative fentanyl and propofol required for maintenance of anesthesia compared to placebo. Patients who received dexmedetomidine showed significant decrease of intraoperative and postoperative mean blood pressure, heart rate. In the postoperative period, dexmedetomidine decreased pain scores and PCA morphine use significantly and showed better recovery profile as compared to the placebo Group. There was no difference in the incidence of postoperative nausea and vomiting (PONV) between both groups.

**Conclusion:** The intraoperative infusion of dexmedetomidine decreased the total amount of propofol and fentanyl required to maintain anesthesia, offered better control of intraoperative and postoperative hemodynamics, decreased postoperative pain level, decreased the total amount of morphine used and showed better recovery profile compared with placebo.

**Key words:** Obesity; Fentanyl; Dexmedetomidine; Propofol; Pain, postoperative; Morphine.

## Introduction

The increasing incidence of morbid obesity is a crisis in national healthcare, which has precipitated an increase in bariatric surgery<sup>1</sup>. Anesthetic management of morbidly obese patients poses a challenge to the anesthesiologist<sup>2-4</sup>. Prevalence of a difficult airway, risk for aspiration, pulmonary embolus, and consideration of concomitant disease in morbidly obese patients, have been previously described<sup>5-8</sup>. The incidence of obstructive sleep apnea and decreased tissue oxygenation is high in morbidly obese patients, increasing the risk of morbidity and mortality due to inadequate postoperative ventilation<sup>9-11</sup>. Obese patients may be sensitive to the respiratory depressant effect of opioid analgesic drugs and more likely to require postoperative ventilation to avoid hypoxic episodes<sup>12</sup>. It has been recommended that opioid drugs be avoided for analgesia in the morbidly obese patient because of the risk of respiratory depression<sup>13</sup>. This requires that alternative drugs be used in place of

opioids to provide analgesia during surgery. Several drugs, including clonidine, ketamine, magnesium, lidocaine, ketorolac, and steroids have all been shown to be analgesic<sup>14-19</sup>.

Dexmedetomidine is a specific  $\alpha_2$ -adrenergic receptor agonist with antinociceptive and sedative properties that has been approved by the Federal Drug Administration for 24-hour sedation in the intensive care unit. Reports indicate that dexmedetomidine decreased anesthetic requirements during surgery, provided postoperative analgesia, and decreased morphine use in the postanesthesia care unit (PACU<sup>20-22</sup>). In addition, dexmedetomidine alone produced minimal respiratory depression<sup>23-24</sup>.

Open Roux-en-Y gastric bypass (RYGBP) has proven to be an effective method for weight control for the morbidly obese patient. With technologic and surgical skill advancement in the application of laparoscopic surgery, laparoscopic RYGBP has also been found to be of value in surgical control of obesity<sup>25</sup>. Benefits of laparoscopic RYGBP, as compared with open RYGBP, include decreased postoperative pain, reduction of postoperative pulmonary dysfunction, less intraoperative blood loss, shorter intensive care and hospital stays, and an earlier return to daily activities<sup>4</sup>.

The choice of anesthetic technique for general anesthesia in morbidly obese patients remains controversial<sup>26</sup>. We hypothesize that the use of dexmedetomidine for facilitation of anesthesia in patients receiving total intravenous anesthesia (TIVA) for laparoscopic RYGBP will offer intraoperative control of blood pressure and heart rate, decrease the total amount of propofol and fentanyl required to maintain anesthesia, decrease the amount of postoperative opioids used and offer better recovery profile. The decrease in postoperative opioids use in dexmedetomidine-treated patients may be important for attenuating the risk of narcotic-induced postoperative respiratory depression and hypoxemia in patients after laparoscopic RYGBP surgery.

## Patients and Methods

After obtaining approval of the local Ethics Committee and patients

informed signed consent for elective laparoscopic Roux-en-Y gastric bypass (RYGBP) surgery, and following discussion with a team of clinicians, 80 morbidly obese patients (ASA physical status II or III and age 26 to 55 years) were enrolled. Patients with clinically significant brain, cardiac, respiratory, or liver disease were excluded.

Patients were randomized to receive either placebo (Group P, n = 40) or dexmedetomidine (Group D, n = 40) for facilitation of intraoperative anesthesia. Patients and investigators recording data in the operating room were blinded to the treatment with either placebo or dexmedetomidine but the anesthesiologist was aware of the treatment condition. The same surgeon performed all of the surgeries.

All drug doses were determined according to true patient weight. In all patients, antithrombotic treatment with low molecular weight heparin was started 12 hours before the operation. All patients were given midazolam 3-mg with glycopyrrolate 0.2 mg intravenous bolus in the holding area.

In the operating room, standard anesthesia monitoring was applied: ECG, non-invasive blood pressure, pulse oxymetry, EtCO<sub>2</sub> (end-tidal CO<sub>2</sub>), peripheral nerve stimulator, temperature probe, spirometry and urinary catheter to measure the urine volume. In order to control the depth of anesthesia, BIS (bispectral analysis of EEG, Aspect Medical, USA) monitoring was used.

Intravenous premedication consisted of 10 mg of metoclopramide, 50 mg of ranitidine, and 8 mg of dexamethazone. In all patients anesthesia was induced with fentanyl (0.5 µg/kg), lidocaine (100 mg), and propofol (1-2 mg/kg). For facilitating endotracheal intubation, cisatracurium was administered at an initial dose of 0.2 mg/kg followed by boluses of 0.03 mg/kg every 20-40 minutes based on neuromuscular stimulation. The patients' lungs were ventilated with a mixture of 50% air in oxygen in the pressure control mode with a positive end-expiratory pressure of 5-10 cm H<sub>2</sub>O to maintain normocapnia (EtCO<sub>2</sub> 35-45 mmHg). For maintenance anesthesia, continuous infusion of propofol 10 mg/kg/h was started; the rate of propofol was changed to maintain the BIS level between 40 and

60. In Group D, dexmedetomidine ( $0.8 \mu\text{g}/\text{kg}$ ) (Precedex, Abbot Laboratories Inc., Abbot Park, IL, USA) was given intravenously over 10 minutes as a loading dose, then infused at a rate of  $0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  as indicated in the package insert. In Group P, normal saline instead of dexmedetomidine was given in the same volume (ml) and rate (ml/hr). In both groups, fentanyl ( $0.5 \mu\text{g}/\text{kg}$ ) boluses were given if blood pressure or heart rate showed 20% increase from the base line reading to control the hemodynamics. All patients in both groups received a total volume infusion of 3-4 L of Ringer's lactate solution during anesthesia. The infusion of both placebo (saline) and dexmedetomidine was completed till the removal of laparoscopy ports.

Patients were placed in the semi-lithotomy position. Laparoscopic RYGBP was performed through five abdominal trocars. Intra-abdominal pressure was maintained at 15 mmHg. A small gastric pouch (20-30 ml) was created using several ENDO GIAs. The small bowel was divided 50 cm distal to the duodenojejunal junction (DJ), and then the distal end was brought up to the newly created gastric pouch using linear stapler 45 mm blue cartilage to create the gastrojejunostomy, the enterotomy closed hand sewn using 2/0 Ethibond. We then measured 150 cm of small bowel just distal to the gastrojejunostomy (Alimentary Limb) to be reconnected to the divided small bowel (Biliopancreatic limb) using linear stapler 60 mm white cartilage to create jejunojunctionostomy, the enterotomy closed hand sewn using 2/0 Ethibond. The anastomosis was oversewn with interrupted sutures, inspected endoscopically, and tested for air leaks.

At the end of surgery, anesthesia was maintained at a constant level during closure of the surgical incisions until the last stitch was completed. Propofol was then turned off and the time to extubation was recorded. At the end of the operation, muscle relaxation was reversed based on the peripheral nerve stimulation. The extubation was performed when the patient gained at least 80% on Train-of-Four stimulation. All patients were extubated and transferred to the postoperative acute care unit (PACU), and standard postoperative monitoring of the vital functions was instituted: ECG, non-invasive blood pressure, and continuous pulse

oximetry. Patients were given oxygen 2-3 l/min via nasal catheter.

In the postoperative care unit (PACU), subjective patient pain scores were obtained with a scale from 0 to 10 with 0 = no pain and 10 = worst pain at 1 and 2 hours and blood pressure and heart rate at 1 hour of recovery, by a nurse blinded to the treatment procedure. Patient-controlled analgesia (PCA) using morphine for pain control was started in the PACU once the patient became alert. Patients were encouraged to ambulate on postoperative day (POD) 1. Postoperative pulmonary care included incentive spirometry and deep breathing exercises.

Mean blood pressure and heart rate were determined every 5 minutes during surgery. Total time of anesthesia and that of surgery were recorded. Bispectral index, the total amount of propofol used (mg) and the total amount of intraoperative fentanyl were measured every hour. Total amount of morphine used in the postoperative period was calculated. The profile of recovery after anesthesia including the duration to spontaneous respiration, adequate respiration (Negative Inspiratory Force NIF >50 cmH<sub>2</sub>O, tidal volume >500 ml, saturation on oxygen >98%) and safe extubation were compared between the 2 groups. The incidence of postoperative nausea and vomiting (PONV) was recorded.

### *Statistical Analysis*

Data were expressed as means and standard deviation. Repeated measures ANOVA and Student's t test were used for each parameter for within and between group comparisons. Pain score and incidence of side effects were compared using Wilcoxon signed ranks test. P value of <0.05 was considered significant. All statistical analysis was performed using Excel and SPSS package.

### **Results**

Eighty patients were enrolled in the study and no dropouts occurred. Patient demographics are shown in Table 1. There was no difference in

age, weight, height, body mass index, sex, ASA physical status, or duration of the procedure between the two groups.

*Table 1*  
 Patient age, weight, height, body mass index, sex, ASA physical status and duration of the procedure in minutes (mean ± SD).

	<b>Group P</b> <b>Placebo (n = 40)</b>	<b>Group D</b> <b>Dexmedetomidine (n = 40)</b>
Age (y)	29 ± 8	30 ± 6
Weight (kg)	119 ± 21	123 ± 27
Height (cm)	168 ± 8	169 ± 10
BMI (kg/m <sup>2</sup> )	42 ± 5	43 ± 6
Sex (M/F)	(18/12)	(16/14)
ASA (PS)	II (24), III (16)	II (26), III (14)
Duration of the procedure (min)	155 ± 27	157 ± 29

ASA (PS) = ASA physical status with number of patients in parenthesis; BMI = body mass index.

During anesthesia, mean arterial blood pressure (Fig. 1) and heart rate (Fig. 2) were significantly decreased in the dexmedetomidine compared with the placebo group.

*Fig. 1*  
 Changes in mean arterial blood pressure (mmHg) between the two groups  
 \*  $P < 0.05$  in Dexmedetomidine group compared to placebo group.

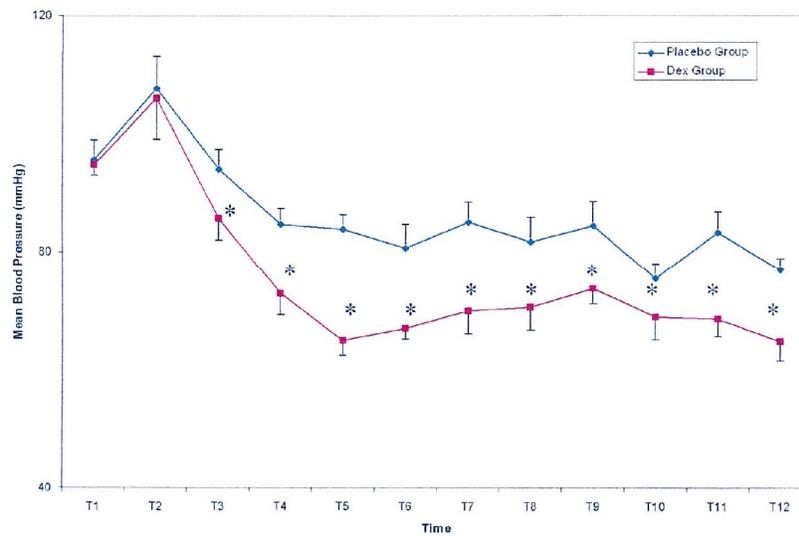
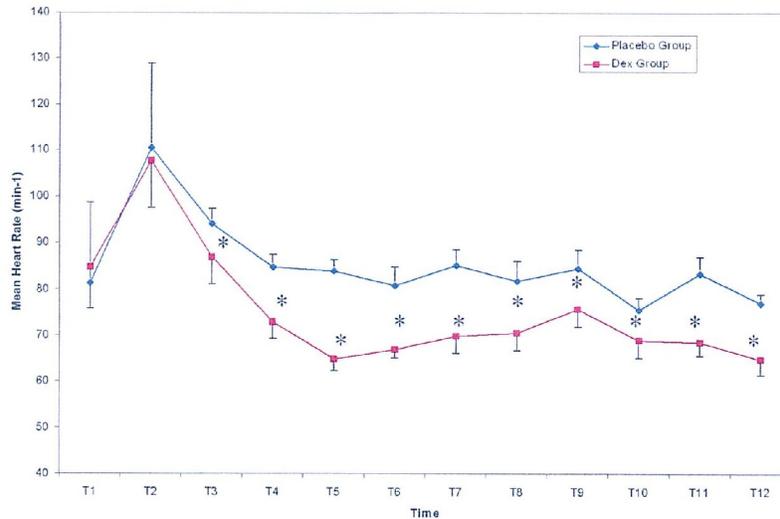


Fig. 2  
 Changes in mean heart rate ( $\text{min}^{-1}$ ) between the two groups  
 \*  $P < 0.05$  in Dexmedetomidine group compared to placebo group.



The total amount of propofol required to maintain the target BIS level was significantly lower in the dexmedetomidine group compared with the placebo group. The total amount of intraoperative fentanyl required to maintain the hemodynamics was significantly lower in the dexmedetomidine compared with the placebo group. The total amount of PCA morphine at two hours in the PACU and POD1 were significantly lower in the dexmedetomidine compared with the placebo group. Pain scores at one hour and two hours, blood pressure, and heart rate were significantly lower in the dexmedetomidine group in the PACU (Table 2).

Table 2  
Measurements made at the end of surgery (mean  $\pm$  SD)

	Placebo (n = 40)	Dexmedetomidine (n = 40)
PACU pain score (0-10, 1 h)	6 (5-8)	3 (2-4)*
PACU pain score (0-10, 2 h)	5 (2-5)	2 (1-3)*
PACU morphine (mg, 2 h)	10.2 $\pm$ 1.3	5 $\pm$ 1.4*
Total amount of morphine (mg, PODI)	47.8 $\pm$ 8	35.4 $\pm$ 6.4*
PACU mean blood pressure (mmHg, 1 h)	91 $\pm$ 11	71 $\pm$ 11*
PACU heart rate (min <sup>-1</sup> , 1 h)	87 $\pm$ 11	71 $\pm$ 8*
Total amount of intraoperative fentanyl ( $\mu$ g)	362.2 $\pm$ 57.2	199.4 $\pm$ 44.6*
Total amount of intraoperative propofol (mg)	2162 $\pm$ 454	1447 $\pm$ 310*

\*  $P < 0.05$  in Dexmedetomidine group compared to placebo group.

**Recovery Profile:** Duration to spontaneous respiration, adequate respiration and safe extubation were significantly shorter in the dexmedetomidine group compared with the placebo group. These durations starts from end of surgery and discontinuation of propofol infusion (Table 3).

Table 3  
Recovery profile in minutes (mean  $\pm$  SD)

	Placebo (n = 40)	Dexmedetomidine (n = 40)
Response to verbal command	3.9 $\pm$ 1.2	3.5 $\pm$ 0.6
Spontaneous respiration	4.6 $\pm$ 1	3.3 $\pm$ 0.4*
Adequate respiration	6.8 $\pm$ 1.6	4.1 $\pm$ 0.5*
Safe extubation	7.5 $\pm$ 1.3	5.1 $\pm$ 0.7*

\*  $P < 0.05$  in Dexmedetomidine group compared to placebo group.

All patients after extubation were fully awake, in respiratory and circulatory efficiency. There was no difference in the incidence of postoperative nausea and vomiting (PONV) between both groups (Table 4).

Table 4  
Incidence of PONV. Data is presented as number (%)

	Placebo (n = 40)	Dexmedetomidine (n = 40)
No nausea and vomiting	37 (92.5%)	38 (95%)
Nausea	3 (7.5%)	2 (5%)
Vomiting	0 (0%)	0 (0%)

## Discussion

The results of this study showed that the use of dexmedetomidine decreased the total amount of intraoperative fentanyl and propofol required for maintenance of anesthesia during laparoscopic gastric bypass procedures. Patients received dexmedetomidine showed better control of intraoperative and postoperative mean blood pressure, heart rate. In the postoperative period, dexmedetomidine decreased pain scores and PCA morphine use and showed better recovery profile compared with placebo.

Ten percent of morbidly obese patients have severe respiratory impairment such as obesity hypoventilation syndrome<sup>27</sup> while over 50% have moderate or severe sleep apnea<sup>28</sup>. Upper abdominal surgery is a risk for impaired pulmonary function after surgery and this effect is compounded by the elevated rate of obstructive sleep apnea in morbidly obese patients<sup>10-11</sup>.

Laparoscopic RYGBP is a complex upper abdominal operation requiring advanced laparoscopic surgical dissection, advanced laparoscopic stapling skill, advanced laparoscopic intracorporeal suturing technique, and all performed in an environment of copious extra- and intraabdominal adipose tissue<sup>4</sup>. Laparoscopic RYGBP is not only a technically difficult operation but also requires experience in preoperative and postoperative management of morbidly obese patients.

The problem of respiratory depression and postoperative hypoxia in obese patients undergoing laparoscopic RYGBP is magnified by the use of narcotics during surgery and the need for opioids for postoperative pain control<sup>29</sup>. Opioids can be associated with potentially pronounced respiratory depressant effects in morbidly obese patients with OSA. Therefore, this patient population could benefit from a drug that can produce analgesic effects without significant or long-lasting effects on

respiratory function.

Although other nonopioid drugs have been used to replace fentanyl during gastric bypass surgery in morbidly obese patients<sup>30</sup>, the development of dexmedetomidine, a highly specific  $\alpha_2$ -adrenergic agonist with an eight times higher affinity for the  $\alpha_2$ -adrenoceptor than clonidine, produced a class of sedative/analgesic drugs that could have advantages for the perioperative management of the obese patient. Dexmedetomidine, with sedative/hypnotic, anesthetic-sparing, analgesic, and sympatholytic properties, has been approved for use in the management of patients in the ICU<sup>31-32</sup>; however, its role in contemporary intraoperative anesthesia practice has not yet been fully established.

The ability of dexmedetomidine to decrease anesthesia requirements, better control of heart rate and blood pressure, and provide analgesia without respiratory depression has been reported before<sup>20-22</sup>. When infused at rates of 0.2 and 0.7  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ , dexmedetomidine produced clinically effective sedation and reduced the analgesic requirements of ventilated ICU patients<sup>33</sup>. There was no clinically apparent respiratory depression after cessation of assisted ventilation, while at the same time dexmedetomidine maintained a high degree of patient arousability<sup>33</sup>. Aho et al.<sup>34</sup> showed that, after laparoscopic tubal ligation, dexmedetomidine relieved pain and reduced opioid requirements. In a subsequent study<sup>35</sup>, the same authors confirmed that dexmedetomidine infusion diminished isoflurane requirement by >90%. When used in the ICU setting and given to intubated patients, dexmedetomidine resulted in 80% less use of midazolam, and 50% less use of morphine compared with the control group<sup>36</sup>. In another study, dexmedetomidine reduced propofol requirements during bispectral index-guided sedation in the ICU and reduced morphine requirements by over 50%<sup>37</sup>. This is in agreement with the recent report by Arain et al.<sup>38</sup> who demonstrated a 66% reduction of postoperative morphine requirements when using dexmedetomidine.

The beneficial use of dexmedetomidine in Roux-en-Y gastric bypass surgery has been previously studied by other authors. Dresel et al.<sup>39</sup> showed that dexmedetomidine has shown a significant decrease in the use of narcotics and respiratory suppression when used for acute pain management after Roux-en-Y gastric bypass patients. Hofer et al.<sup>1</sup>

reported a morbidly obese patient whose intraoperative narcotic management was substituted entirely with dexmedetomidine. The narcotic sparing effects of dexmedetomidine were evident both intraoperatively (low isoflurane requirements) and postoperatively (lower total dose of self-administered PCA morphine). Feld et al.<sup>40</sup> showed that dexmedetomidine could be used in place of fentanyl for intraoperative control of blood pressure and heart rate during open gastric bypass surgery. Dexmedetomidine treatment required less desflurane than fentanyl to maintain anesthesia.

Our results confirm these previous reports and have shown that dexmedetomidine infusion reduced propofol requirements by 33% during bispectral index-guided anesthesia and resulted in 45% less use of intraoperative fentanyl compared with placebo. Our study showed similar results to the previous studies whereby dexmedetomidine decreased pain scores in PACU and decreased postoperative PCA morphine use by 50% in the first two hours and by 26% at the end of postoperative day one compared with placebo.

Our study showed better recovery profile in the dexmedetomidine treated patients compared with placebo which can be explained by the fewer amounts of intraoperative fentanyl and propofol required to maintain anesthesia in this group of patients. Because a primary effect of dexmedetomidine is to decrease sympathetic activity<sup>20</sup>, it was expected that the  $\alpha_2$ -adrenergic agonist would be effective in controlling intraoperative blood pressure. Our data confirm that dexmedetomidine decreased blood pressure and heart rate compared with a placebo infusion.

**In conclusion**, the intraoperative infusion of dexmedetomidine may be an attractive option during laparoscopic RYGBP surgery as it decreased the total amount of propofol and fentanyl required to maintain anesthesia, offered better control of intraoperative and postoperative hemodynamics, decreased postoperative pain level and decreased the total amount of morphine used compared with placebo, thus attenuating the risk of narcotic-induced postoperative respiratory depression and hypoxemia in morbidly obese patients.

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