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Research Article

The effect of combined remifentanil and low dose ketamine infusion in patients undergoing laparoscopic gastric bypass

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KEYWORDS

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Abstract *Background:* The choice of anesthesia in morbidly obese patients remains controversial. We evaluated the effect of continuous low dose ketamine infusion combined with remifentanil and propofol in patients undergoing laparoscopic gastric bypass, on hemodynamic stability, postoperative analgesic requirement and recovery profile.
Methods: 60 patients aged 25–50 years, allocated into 2 groups. Group I: received continuous infusion of (propofol 6–10 mg/kg/h + remifentanil 0.2 μg/kg/min + saline). Group II: received continuous infusion of (propofol 6–10 mg/kg/h + remifentanil 0.2 μg/kg/min + ketamine 1μg/kg/min). All patients recieved intravenous morphine by patient controlled analgesia (PCA) postoperatively. Mean blood pressure and HR, duration of anesthesia and surgery recorded. Bispectral index, total amount of propofol and remifentanil used intraoperative were measured. In the recovery room, time to response to verbal commands was recorded, subjective pain scores were obtained with a scale from 0–10. Postoperative nausea and vomiting, hallucinations were recorded. Early pain perception and total consumption of morphine in 24 h recorded.
Results: During anesthesia, mean arterial blood pressure and heart rate were decreased in group I compared with group II. The amount of propofol required to maintain the target BIS was lower in group II compared with group I . The amount of intraoperative boluses of remifentanil required to

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maintain hemodynamics was lower in group II compared with group I. The amount of PCA morphine at 2 h in the PACU and the first post operative day were lower in group II compared with group I. Pain scores at 1 h and 2 h postoperatively were lower in group II compared to group I. P value < 0.05 was considered significant.

Conclusion: During laparoscopic gastric bypass in morbidly obese patients the co-administration of low dose ketamine and remifentanil by continuous infusion provide more hemodynamic stability, satisfactory recovery profile and adequate postoperative pain relieve.

1. Introduction

The increasing incidence of obesity is a growing problem in national health care, which causes an increase in bariatric surgery [1]. Obese patients may be sensitive to respiratory depressant effect of opioid analgesic drugs and are more likely to require postoperative ventilation to avoid hypoxic episodes [2]. Remifentanil hydrochloride, an ultra-short acting mu opioid receptor agonist, because of its ester structure, remifentanil is submitted to wide spread ester hydrolysis, resulting in very rapid metabolism [3]. It is now currently used with propofol as total intravenous anesthesia (TIVA), it appears to produce moderate to mild hypotension [4]. Also an important concern with remifentanil is the possibility of acute opioid tolerance or hyperalgesia that may increase postoperative pain [5]. Ketamine, a dissociative intravenous anesthetic. It was first used in human in 1965, it remains the subject of interest in clinical investigations [6]. The choice of general anesthesia for obese patients remains controversial [7].

The aim of this study was to evaluate the efficacy of continuous low dose ketamine infusion combined with remifentanil and propofol infusion (TIVA) in patients undergoing laparoscopic Roux-en-Y gastric bypass (RYGBP), on hemodynamic stability, postoperative analgesic requirement and recovery profile.

2. Patients and methods

After approval of the local Ethics Committee and patients informed written consent for elective laparoscopic Roux-en-Y gastric bypass (RYGBP) surgery, 60 morbidly obese patients (ASA physical status II or III), and age between 25 and 50 years, were enrolled in the study.

Patients with significant cardiac, respiratory, brain, liver or kidney diseases, or patients having allergy to the study drugs or patients unable to use post operative PCA were excluded from the study.

The patients were randomly allocated into two equal groups. Group I: received continuous infusion of (propofol 6–10 mg/kg/h guided by the BIS + remifentanil 0.2 μg/kg/min + saline). Group II: received continuous infusion of (propofol 6–10 mg/kg/h guided by the BIS + remifentanil 0.2 μg/kg/min + ketamine 1 μg/kg/min). All patients were planned to receive intravenous morphine patient controlled analgesia (PCA) postoperatively. PCA morphine prepared by adding 30 mg morphine sulphate to 27 ml normal saline, total volume 30 ml at concentration 1mg/ml, no bolus injection, PCA bolus 1 ml, no background infusion, lockout period 10 min, total amount of morphine in 4 h is 24 ml.

Patients and investigators recording data in the operating room were blinded to the treatment (ketamine or placebo), but anesthesiologist were aware of the treatment condition.

All drug doses were used according to true patient weight. In all patients antithrombotic treatment with low molecular weight heparin was started 12 h before the procedure. All patients received midazolam 3 mg with glycopyrrolate 0.2 mg intravenous bolus in the holding area.

In the operating room, standard monitors were applied: ECG, non invasive blood pressure, pulse oximetry, $EtCO_2$ (end tidal CO_2), peripheral nerve stimulator, temperature probe, spirometry, urinary catheter and BIS (bispectral analysis of EEG, Aspect Medical, USA).

Before induction of anesthesia, patients received 10 mg metoclopramide, 50 mg ranitidine, and 8 mg dexamethazone i.v.

Anesthesia was induced after pre-oxygenation for 3 min by face mask with 100% oxygen, by remifentanil (1 μg/kg), lidocaine (100 mg), propofol (1–2 mg/kg), and cisatracurium to facilitate endotracheal intubation (0.2 mg/kg).

The lungs were ventilated with a mixture of 50% air in oxygen in the pressure control mode with positive end-expiratory pressure (5–10 cm H_2O) to maintain normocapnea ($EtCO_2$ 35–40 mm Hg).

For maintenance of anesthesia, continuous infusion of propofol 6–10 mg/kg/h was started; the rate of propofol was changed to maintain the BIS between 40 and 55.

In group I: remifentanil infusion in dose of (0.2 μg/kg/min) was added.

In group II: combined infusion of remifentanil (0.2 μg/kg/min) + ketamine (1 μg/kg/min) were added.

Cisatracurium given to all patients by boluses to maintain muscle relaxation (0.03 mg/kg) every 20–40 min based on neuromuscular stimulation.

All patients received a total volume of infusion of 3–4 L of Ringer's Lactate solution during anesthesia.

The infusions of both remifentanil, saline in (group I) and remifentanil, ketamine in (group II) were continued till removal of laparoscopy ports.

Patients were placed in the supine position. Laparoscopic RYGBP was performed through five abdominal trocars. Intra-abdominal pressure was maintained at 15 mm Hg.

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 safe extubation was recorded. At the end of the operation muscle relaxant was reversed based on peripheral nerve stimulation. The extubation was performed when the patient gained 80% on Train-of-four stimulation. All patients were extubated and sent to

post anesthesia care unit (PACU), and standard post operative monitoring of the vital signs were applied: ECG, non invasive blood pressure, pulse oximetry, 2–3 L/min oxygen by nasal cannula were applied to all patients.

In the recovery room, time to response to verbal commands was recorded, subjective pain scores were obtained with a scale from 0 to 10, with 0 = no pain and 10 = worst pain, at 1 and 2 h post operatively by a nurse blinded to the study protocol.

Morphine patient controlled analgesia (PCA) was started once the patient pain score recorded 1–2 and continued in the ward for 24 h postoperative.

Patients were encouraged to ambulate in the first post operative day. Post operative pulmonary care included incentive spirometry and deep breathing exercises were encouraged.

3. Measurements

Mean blood pressure (mm Hg) and HR (beats/min) were measured before induction and every 5 min during surgery (recorded data T0: preoperative measures, T1 immediately after induction, T2: 5 min after induction, T3: 10 min after induction, T4: 15 min after induction, T5: 30 min after induction, T6: 60 min after induction, T7: 90 min after induction, T8: 2 h after induction, T9: 1st postoperative hour, T10: 2nd postoperative hour, T11: 6 h post operative, T12: 12 h post operative). Duration of anesthesia and surgery (min) were recorded. Bispectral index, total amount of propofol used (mg) and total amount remifentanil used intraoperative were measured every hour. Total amount of morphine used in the 24 h postoperative period was calculated. The recovery profile after anesthesia including: time to spontaneous respiration, adequacy of respiration (Negative Inspiratory Force (NIF) > 50 CmH_2O, tidal volume > 500 ml, saturation on O_2 > 98%) was recorded.

The incidence of postoperative nausea and vomiting (PONV), hallucinations were recorded and managed accordingly.

Early pain perception was measured by the time that passed between extubation and the first request of PCA (min). The outcome was the consumption of morphine by intravenous titration and by PCA during the first 4 h after surgery. Prolonged perception of pain was measured by patients' total consumption of morphine (mg) in 24 h.

4. Statistical analysis

Data were expressed as mean ± standard deviation. Student's *t* test was used for each measurement within and between group comparisons. Pain score and the incidence of side effects were compared using Chi square test. *P* value of <0.05 was considered significant. All statistical analysis were done using Excel and SPSS package.

5. Results

Sixty patients were enrolled in the study with no exclusion. Patients demographic data are shown in Table 1. There were no differences in age, weight, height, body mass index, sex, ASA physical status or the duration of the operation between the two groups.

During anesthesia, mean arterial blood pressure (Fig. 1) and heart rate (Fig. 2) were significantly decreased in group I compared with group II, $P < 0.05$.

The total amount of propofol required to maintain the target BIS was significantly lower in group II compared with group I, $P < 0.05$.

The total amount of intra-operative boluses of remifentanil required to maintain hemodynamic was significantly lower in group II compared with group I.

The total amount of PCA morphine at 2 h in the PACU and the first post operative day were significantly lower in group II compared with group I.

Pain scores at 1 h and 2 h postoperatively were significantly lower in group II compared to group I.

Blood pressure and heart rate at 1 h and 2 h postoperatively were clinically lower in group I compared to group II, but these differences were statistically not significant (Table 2).

Recovery profile, duration to spontaneous respiration, adequate respiration and safe extubation were shorter in group I compared to group II .These duration were statistically

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

	Group I (n = 30)	Group II
Age (y)	27 ± 8	29 ± 6
Weight (kg)	119 ± 14	121 ± 19
Height (cm)	160 ± 5	162 ± 7
BMI (kg/m^2)	40 ± 7	42 ± 4
Sex (M/F)	17/13	15/15
ASA (PS)	II (20), III (10)	II (18), III (12)
Duration of the procedure (min)	159 ± 27	156 ± 31

ASA (PS) = ASA physical status; BMI = body mass index.

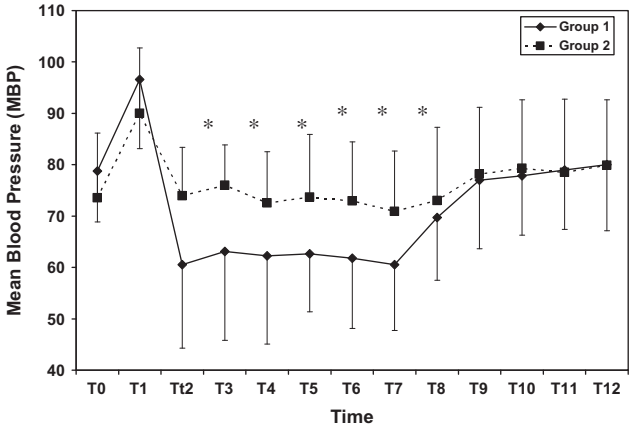

Figure 1 Mean arterial blood pressure changes (mm Hg) in both groups, intraoperative and postoperative. $^*P$ value <0.05 in group 2 compared to group 1. t0: preop data, t1: immediately after induction, t2: 5 min after, t3: 10 min after induction, t4: 15 min after induction, t5:30 min, t6: 60 min, t7: 90 min, t8: 2 h, t9: 1st postoperative hour, t10 2nd hour postoperative, t11: 6 h postoperative, t12: 12 h postoperative. T0, T1: not significant, T2–T7: significant, T8–T12: lower in Group1 but not significant.

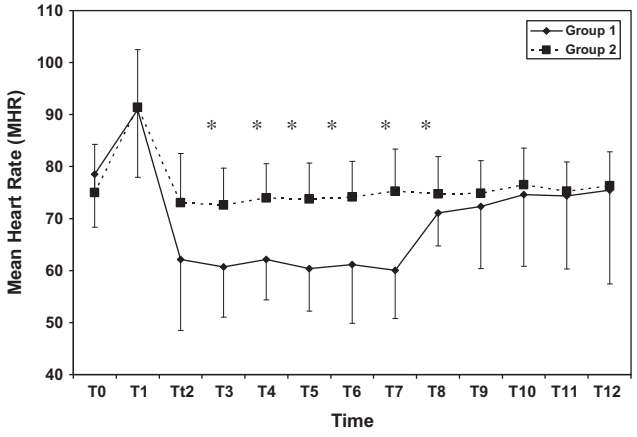

Figure 2 Mean heart rate changes (beats/min) in both groups, intra-operative and postoperative. *P value <0.05 in group 2 compared to group 1. t0: preop data, t1: immediately after induction, t2: 5 min after, t3: 10 min after induction, t4: 15 min after induction, t5: 30 min, t6: 60 min, t7: 90 min, t8: 2 h, t9: 1st postoperative hour, t10 2nd hour postoperative hour, t11: 6 h postoperative, t12: 12 h postoperative. T0, T1: not significant, T2–T7: significant, T8–T12: lower in Group1 but not significant.

Table 2 Measurements made at the end of surgery (mean ± SD).

	Group I (n = 30)	Group II (n = 30)
PACU pain score (0–10) 1 h	6 (4–8)	3 (1–2)*
PACU pain score (0–10) 2 h	5 (2–5)	2 (1–3)*
PACU morphine (mg, 2 h)	10.4 ± 1.4	6.3 ± 10.6*
Total amount of morphine (mg), first 24 h postoperatively	47.4 ± 8	6.1* ± 40
PACU mean blood pressure (mm Hg/h)	90 ± 1	77 ± 9
PACU heart rate (min/h)	91 ± 4	83 ± 4
Total amount of intra-operative remifentanil (μg)	350.5 ± 54.6	201.4 ± 54.3*
Total amount of intra-operative propofol (mg)	2200 ± 450	1503 ± 311*

* $P < 0.05$ in group II compared to group I.

significant (P value <0.05) but clinically not significant. This duration started from end of surgery and discontinuation of propofol infusion (Table 3).

All patients after extubation were fully awake.

No differences in the incidence of postoperative nausea and vomiting or hallucination between both groups (Table 4).

6. Discussion

The problem of postoperative respiratory complications in obese patients is magnified by the use of narcotics during surgery and postoperative for pain control [8].

Opioids can cause pronounced respiratory complications in obese patients with obstructive sleep apnea.

Theoretically, co-administration of an opiate and ketamine decreases the doses needed for optimal analgesia below the required value of opioids when used alone and hence may decreases the incidence of side effects.

Table 3 Recovery profile in minutes (mean ± SD).

	Group I (n = 30)	Group II (n = 30)
Response to verbal commands	3.4 ± 1.2	4.1 ± 0.7
Spontaneous respiration	4.6 ± 1	5.1 ± 0.5*
Adequate respiration	6.1 ± 1.5	6.3 ± 0.7
Safe extubation	7.5 ± 1.3	7.1 ± 0.7

* $P < 0.05$ in group II compared to group I.

Table 4 Incidence of side effects in both groups.

	Group I (n = 30)	Group II (n = 30)
No nausea and vomiting	27 (90%)	28 (93.4%)
Nausea	3 (10%)	2 (6.6%)
Vomiting	0 (0%)	0 (0%)
Hallucination	0 (0%)	0 (0%)

Data are presented as numbers (percentage).

The results of our study showed that, ketamine (1 μg/kg/min) when added to propofol-remifentanil during laparoscopic RYGBP, counteracted the hemodynamic changes induced by remifentanil, decreased propofol consumption, decreased pain score in the postoperative period, decreased morphine PCA consumption and also resulted in a better recovery profile than using remifentanil-propofol alone.

Ketamine-related side effects such as hallucinations, unpleasant dreams, and delirium did not occur in our patients, as we used low dose continuous infusion, such side effects have been related to large doses used for general anesthesia.

In the group received remifentanil alone patients developed hypotension and bradycardia most probably due to remifentanil.

Previous studies have shown an unacceptable incidence of bradycardia associated with the use of remifentanil in the absence of a vagolytic agent [9]. However, opioid-induced bradycardia is gradually accepted to be vagally mediated [10].

It could be due to the impairment of baroreflex regulatory mechanisms caused by propofol infusion [11].

Hypertension and bradycardia have been found with the use of remifentanil when combined with intravenous agent [12] or general anesthetics [13].

In contrast, to these results Glass et al. found increased arterial blood pressure and heart rate after injecting remifentanil intravenously alone without any other agents, in healthy un-premeditated volunteers [14].

Degaute et al. found that remifentanil hydrochloride causes consistent and maintained hypotension [15].

Sammons, AW et al. found profound hypotension caused by remifentanil when compared to fentanyl used for day case microlaryngoscopy [16].

In our study, in the ketamine-remifentanil group the heart rate and mean arterial blood pressure did not decrease below the preoperative values, most probably due to the catecholamine release of ketamine, which is commonly resulting in both tachycardia and hypertension [17], an action that can attenuate remifentanil effects.

In agreement of our study, Katz et al. found that using alfentanil with ketamine resulted in obtunding the tachycardia and hypertension caused by ketamine after intubation and little or no change in HR or ABP [18].

In the postoperative period, the hemodynamic measurements were maintained within normal values in the ketamine-remifentanil group, while in the patients received remifentanil alone there was slight increase in mean blood pressure, which could be explained by the counteracting effect of ketamine on remifentanil induced hyperalgesia.

Regarding recovery from anesthesia, the remifentanil group patient recovered quicker than ketamine-remifentanil group, although it was statistically significant; clinically it was not significant. This is due to the short half-life of remifentanil which is 8–10 min [14]. The presence of an ester side chain allow rapid breaking down of remifentanil by non-specific estrases to nearly inactive metabolites, causing rapid recovery from intraoperative infusion [19].

The time to the first PCA dose required in the PACU, was shorter in the remifentanil group than in the ketamine-remifentanil group, this could be due to the hyperalgesia and the development of opioid-induced tolerance related to remifentanil infusion. This is due to the activation of N-methyl-D-aspartate (NMDA) receptors in the CNS, and subsequent biochemical process leading to central sensitization, increase spinal dynorphin activity and activation of intracellular protein kinase C^{29} [20].

Ketamine, a NMDA receptor antagonist used in the ketamine-remifentanil group may substantially enhance opiate-induced anti-nociception [20].

Frederic Adam and his colleagues [21], evaluated the effect of 1.5 μg/kg/min ketamine for postoperative pain relieve and total consumption of morphine after total knee arthroplasty. They found that ketamine group required less morphine than the control group which helped in early knee mobilization.

Subra Maniam [22], concluded that the addition of ketamine either intravenous bolus or continuous infusion is more effective than morphine alone, while intravenous PCA of ketamine and morphine was not more effective than intravenous PCA morphine alone.

The result of the present study showed that continuous intra-operative infusion of low dose ketamine combined with remifentanil resulted in less postoperative pain score and less morphine consumption than using remifentanil infusion alone. Ketamine may produce its anti-nociception by activation of the descending pain inhibitory mono-aminergic pathways [23], which is expressed by alpha-2-adrenoceptor at the spinal level [24]. Although anti-nociception of ketamine intra-thecal in rats is reversed by naloxone [23], analgesia in humans by systemic ketamine up to 300 μg/kg, cannot be reversed [25], which means that mono-aminergic activation, more than the mu receptor agonist activity, may be present in the anti-nociception effect produced by the analgesic dose of ketamine.

The affinity of ketamine for NMDA receptors is more than an order of magnitude higher than that for mu receptors [25] and several-fold higher than that for monoamine transporter sites or other non-NMDA receptors (i.e. Acetylcholinestrase and the epsilon receptors) [26], suggesting that the smaller the dose, the more selective is the ketamine interaction with NMDA receptors.

In consistent of our study Stubhug et al., showed that in human continuous infusion of small-dose ketamine for 48 h, increases the time for first use PCA-morphine and reduced cumulative morphine [27].

Other studies have found that a marked decrease in consumption of opiate and/or pain intensity by systemic [28] or epidural [29] co-administration of ketamine and opiates.

In conclusion, our results demonstrated that during laparoscopic RYGBP in morbidly obese patients the co-administration of low dose ketamine and remifentanil by continuous infusion provide more hemodynamic stability, satisfactory recovery profile and adequate postoperative pain relieve.

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