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Ketamine as an Adjuvant to Morphine for Patient Controlled Analgesia in Morbidly Obese Patients

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Intravenous Patient Controlled Analgesia (PCA) with morphine is often used for postoperative analgesia in morbidly obese patients. However, the required doses may increase postoperative respiratory disorders. Adjunction of small doses of ketamine could reduce dose and related side effects. Eighty morbidly obese patients undergoing upper abdominal surgery were randomly assigned to receive (during the postoperative period) either intravenous morphine 1 mg mL^{-1} (morphine group: M group) or morphine with ketamine 1 mg mL^{-1} for each (morphine ketamine group: MK group). Morphine consumption was evaluated by cumulative doses every 8 h for 48 h together with Visual Analogue Scale (VAS) scores at rest and at mobilization. Forced Vital Capacity (FVC) and Forced Expiratory Volume in first second (FEV1) were assessed by spirometric evaluation 24 and 48 h after initiation of PCA. Incidence of adverse effects was reported. cumulative morphine consumption was significantly reduced in morphine Ketamine (MK) group. It was 84 (9) mg vs 66(6) mg 48 h after PCA ($p<0.05$). VAS in both groups were similar at rest and at mobilization. Compared with preoperative values, (FVC) was significantly reduced in M group than MK group: 46% (8) vs 62% (9) ($p< 0.05$) at 24 h and 58 (7) vs 77% (11) ($p<0.05$) at 48 h (FEV1) was 60% (9) vs 81% (7) ($p<0.05$) at 24 h and 62% (6) vs 87% (11) ($p<0.05$) at 48 h after PCA initiation. PaO_2, respiratory rate, and SPO_2 were significantly lower in M group than MK group 32 h after PCA initiation ($p<0.05$). Incidence of nausea and desaturation were significantly higher in M group than MK group ($p<0.05$). Adding small doses of ketamine to morphine for PCA decreased cumulative morphine consumption, improved postoperative respiratory function and was associated with less adverse effects in morbidly obese patients undergoing upper abdominal surgery.

Key words: Ketamine, analgesia, patient controlled analgesia, morbidly obese patients, abdominal surgery, anaesthesia, morphine

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INTRODUCTION

Incidence of morbid obesity is increasing and so, their need for surgery is also increasing. In this population optimal post-operative pain control is of considerable importance because obesity is an independent risk factor for cardiovascular and respiratory complications after surgery (Derzie *et al*., 2000). Moreover, morbidity and mortality of morbidly obese patients after upper abdominal procedures were more than two and half times higher than that of their non obese counterparts (Postlethwait and Johnson, 1972). Few clinical trials have evaluated different types of analgesia in morbidly obese patients after abdominal surgery (Roshanak *et al*., 2003).

The use of epidural analgesia with local anaesthetic and/or opioid provides superior dynamic pain relief (Keblet and Holte, 2001) which in turn improves respiratory function resulting in less postoperative pulmonary complication (Ballantyne *et al*., 1998).

Nevertheless and related to technique difficulties or patients refusal, morphine analgesia is still widely used despite a potential harmful influence on postoperative functions (Stone *et al*., 1999).

The large doses needed to provide an optimal analgesic control may be associated with impairment in pulmonary function that could counteract the analgesic benefit (Catley *et al*., 1985).

Morphine alone is not always successful in this context. Indeed, the nociceptive inputs of patients (especially those in the Surgical Intensive Care Unit (SICU)) have additional sources and severities beyond those created by tissue injuries. Pathological pain states mainly hyperalgesia and allodyna, can be induced. Consequently, morphine may be less effective despite large consumption. This tolerance to morphine is an early process favored by paradoxical nociceptive stimulation (Guillou *et al*., 2003).

The role of N-Methyl D-Aspartate (NMDA) excitatory glutamate receptors has been established in nociceptive transmission (Petrenko *et al*., 2003; Cairns *et al*., 2003). Ketamine is a potent NMDA receptor inhibitor and represents a promising modality in several strategies to prevent pathological pain.

The potential benefit of adding ketamine to morphine for Patient Controlled Analgesia (PCA) has been reported by randomized controlled studies in several types of surgery (Guillou *et al*., 2003; Petrenko *et al*., 2003; Cairns *et al*., 2003; Michelet *et al*., 2007).

The aim of this double blinded, randomized study was to investigate if the addition of ketamine to intravenous morphine for PCA could result in sparing effect in opioid consumption and improvement in postoperative pain and respiratory disorders in morbidly obese patients after upper abdominal surgery.

MATERIALS AND METHODS

This prospective, randomized and double blinded study was conducted at Kasr Al-Aini Hospital (Cairo University Hospital), from 2005 to 2007. After local ethics committee approval, written informed consent was obtained from 80 morbidly obese patients [Body Mass Index (BMI)>35 kg m^{-2}], aged 20-65 years, (ASA I, II) undergoing upper abdominal surgery.

Exclusion criteria included diagnosed obstructive sleep apnea syndrome, history of drug abuse, significant cardiopulmonary disease, renal impairment (serum creatinine >1.5 mg dL^{-1}) abnormal liver enzymes (transaminases>1.5× normal) and patients who are unable to understand the use of Patient Controlled Analgesia (PCA) were also excluded.

Patients were instructed on the use of Visual Analogue Scale (VAS) in the preanaesthetic visit. They assessed pain using (VAS) ranging from 0 (no pain)to 100 (worst imaginable pain).

Baseline measurements of Forced Vital Capacity (FVC) and forced expiratory volume in first second (FEV1) were measured bed-side (using Zan 300 co-infusion spirometry) before surgery.

All patients received midazolam (3 mg) i.v., 30 min. before induction of anaesthesia.

An anaesthetic management was standardized for all patients, performed with fentanyl 1.5 mg kg^{-1} and propofol 2 mg kg^{-1} until loss of consciousness, rocuronium 0.9 mg kg^{-1} of Ideal Body Weight (IBW) was administered while applying cricoid pressure. Trachea was intubated 60 seconds later.

The lungs were ventilated with a mixture of oxygen/air (FiO_2 = 0.5). Tidal volume was set at 10 mL kg^{-1} (IBW) with peak airway pressure kept below 35 cm H_2O. Respiratory rate was adjusted to maintain normocapnia.

Anaesthesia was maintained with isoflurane, fentanyl and rocuronium titrated according to patients needs. Additional analgesia such as nonsteroidal anti-inflammatory drugs, regional or local anaesthetic techniques were not allowed during the operative period.

After the operation, patients were transferred to the Surgical Intensive Care Unit (SICU). Tracheal extubation was postponed until the next morning to ensure adequate ventilation. All patients were mechanically ventilated first with Synchronized Intermittent Mandatory Ventilation (SIMV) followed by Continuous Positive Airway Pressure (CPAP) to allow gradual weaning

During that time patients received incremental doses of morphine (5 mg) and midazolam (2 mg) to control pain and anxiety.

VAS was assessed hourly before initiation of any pain treatment and recorded by the SICU nurse through the night.

Next morning, patients were assessed for possibility of weaning from mechanical ventilation and extubation. After extubation patients were placed in a 30° back-up Fowler position breathing oxygen through face mask to keep their oxygen saturation up to 95%.

All patients received PCA device (P 5000 IVAC-PCAM) containing either morphine 1 mg mL^{-1} (morphine group: M group) or morphine with ketamine 1 mg mL^{-1} each (morphine ketamine group: MK group) as the optimal combination of morphine-ketamine has been reported to be 1:1 (Sveticic *et al*., 2003). The stability of this solution has been tested with success previously at a wide range of PH values for at least 4 days (Schmid *et al*., 2002). Patients were randomized according to closed envelope method.

A nurse not involved in the care of the patients prepared the syringes of morphine or morphine ketamine. Patients were instructed to achieve maximal comfort in order to breathe and cough without substantial pain. They were allowed to have bolus doses of morphine or morphine and ketamine at the dosage of 0.015 mL kg^{-1} IBW at 10 min interval.

If pain control was inadequate, diclofenac 75 mg was administered in order to lower the VAS to less than 40 at mobilization. It was considered as rescue analgesia and recorded as such.

The following variables were recorded and assessed: The 8 h cumulative morphine consumption over 48 h period, the VAS at rest and at mobilization every 8 for 48 h.

Haemodynamic values (Arterial blood pressure, heart rate), respiratory rate and oxygen saturation were continuously monitored and recorded.

Bed-side pulmonary functions (FVC and FEV1) were measured preoperatively and repeated 24 and 48 h after initiation of PCA

Arterial Blood Gases (ABG) were measured every 8 for 48 h. Ramsay score for sedation was recorded 8 h (Table 1).

The following complications (nausea, pruritis, hallucination, dreams, blurred vision, oral secretions, and desaturation<90%) were reported.

Table 1: Modified Ramsay scale for sedation

Score	Description
1	Anxious and agitated or restless, or both
2	Cooperative, oriented and tranquil
3	Drowsy, but responds to commands
4	Asleep, brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to light glabellar tap or loud auditory stimulus
6	Asleep and unarousable

At the end of the study (48 h after initiation of PCA), patients were asked if they were satisfied or not satisfied with regard to the analgesic strategy.

Patients, nurses in charge of postoperative care who monitored the patients, performed analgesia and collected data were blinded to the PCA regimen used.

Statistics: Statistical analysis was performed with Excel and SPSS® statistical package. Data are expressed as mean (SD). Analyses were performed with Mann Whitney U-test for (quantitative variables) and Pearson`s χ^2 test for (qualitative variables).

A two way repeated measures Analysis of Variance (ANOVA) followed by a Tukey`s post hoc test were used to evaluate the effect of time and PCA mixture on morphine consumption.

Forty patients were required in each group to detect a 25% difference in the amount of morphine consumption at the 0.05 level of significance with a power of 0.9. A-value < 0.05 was considered significant.

RESULTS

There were no significant difference across the groups with respect to demographic and perioperative data (Table 2).

Adding ketamine to morphine in PCA device resulted in a significant reduction in cumulative morphine consumption as early as 8 h after initiation of the PCA till the end of the study (Fig. 1).

The mean morphine consumption at 48 h was 84 (9) mg in morphine group vs. 66 (6) mg in morphine ketamine group ($p<0.05$).

This reduction was associated with similar pain scores at rest and at mobilization (Fig. 2, 3).

Table 2: Demographic characteristics and perioperative data. Values are expressed as mean±SD

Characteristics	M group	MK group
	---------n = 40 ---------	
Gender (Male/Female)	22/18	19/21
Age (years)	39±12	38±14
BMI (kg m^{-2})	48±6	49±7
Diabetes mellitus (n) (%)	9 (22.5%)	10 (25%)
Hypertension (n) (%)	7 (17.5%)	8 (20%)
Bronchial asthma (n) (%)	2 (5%)	2 (5%)
Type of surgery (n)		
Gastric by pass	18	17
Gastric stapling	16	19
Paraumbilical hernia repair	6	4
Length of incision (dermatomes)	5±1.6	4±1.7
Duration of surgery (min)	116±16	118±14
Intra-operative fentanyl	186±14	198±11
Incremental doses of morphine before PCA (mg)	12.6±2.1	13.1±1.9
Preoperative FVC (L)	2.8±0.5	2.9±0.4
FEV_1 (L)	2.1±0.2	2.2±0.3
Duration of postoperative mechanical ventilation (h)	17.6±1.2	18.2±1.1

M = Morphine, MK = Morphine ketamine, BMI = Body mass index, VFC = Forced vital capacity, FEV1 = Forced expiratory volume in first second

Table 3: Mean arterial pressure, heart rate, respiratory rate and pulse oximetry before and after PCA

HhVaria variables/Times	Baseline before (PCA)	8 h	16 h	24 h	32 h	40 h	48 h
MAP (mmHg)							
M group	103.0±9	92.0±11	97.0±12	96.0±9	91.0±15	88.0±17	
MK group	104.0±6	97.0±12	94.0±9	93.0±10	96.0±12	90.0±11	
HR (beat min^{-1})							
M group	82.0±14	88.0±13	97.0±16	92.0±18	91.0±11	78.0±9	76.0±9
MK group	84.0±16	84.0±14	79.0±11	88.0±9	86.0±10	81.0±11	79.0±11
RR (breathe min^{-1})							
M group	15.2±4.5	15.7±4.9	15.9±5.4	15.9±3.6	12.3±3.2*	15.4±2.1	15.8±2.2
MK group	17.3±6.8	17.2±4.4	17.3±5.2	16.8±4.2	16.8±2.1*	16.1±2.1	16.2±2.8
SPO_2%							
M group	96.3±2.1	96.5±2.2	94.9±3.1	95.7±2.2	93.1±2.3*	95.7±2.3	95.9±1.8
MK group	96.5±2.3	96.7±2.3	95.5±2.2	96.2±1.8	96.3±2.1*	96.5±2.2	96.5±2.3

MAP = Mean arterial pressure, HR = heart rate, RR = respiratory rate, PCA = patient controlled analgesia, * ($p<0.05$) between groups, Data are mean±SD

Table 4: Arterial blood gas analysis (patients breathing room air)

Variables/Times	Baseline before (PCA)	8 h	16 h	24 h	32 h	40 h	48 h
ABG							
pH							
M group	7.38±0.02	7.39±0.02	7.38±0.03	7.37±0.07	7.38±0.01	7.37±0.02	7.38±0.02
MK group	7.38±0.03	7.38±0.01	7.38±0.02	7.38±0.03	7.39±0.02	7.38±0.03	7.39±0.01
PaO_2 (mmHg)							
M group	8.82±11.2	92.20±3.2	87.31±6.6	88.40±7.6	91.00±7.2*	91.60±11.1	93.90±8.6
MK group	86.32±9.2	93.10±6.1	89.60±7.2	89.20±9.1	98.20±3.1*	96.90±9.2	91.60±3.8
$PaCO_2$ (mmHg)							
M group	39.52±1.6	41.60±2.3	34.69±3.8	46.01±3.1	46.01±3.1	38.60±3.6	36.90±2.3
MK group	43.16±2.1	43.70±1.3	36.21±4.1	42.60±2.6	42.60±2.6	37.10±3.2	36.60±3.1
Saturation (%)							
M group	95.40±3.4	95.80±2.1	95.10±2.9	94.60±2.3	93.10±2.3*	95.50±2.3	95.60±1.7
MK group	94.30±7.6	95.40±3.3	95.20±2.3	94.80±1.8	96.40±1.8*	96.90±2.2	96.80±1.1

*($p<0.05$) between groups, Data are mean±SD

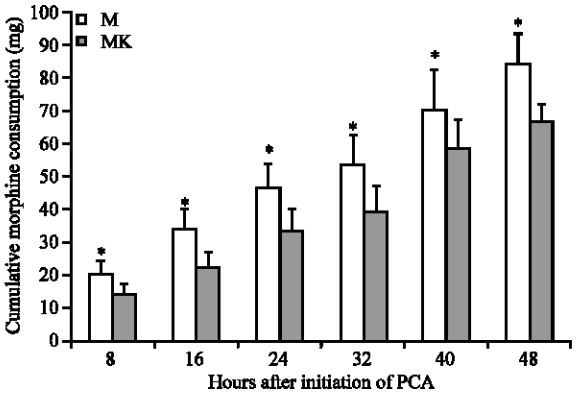

Fig. 1: Cumulative morphine consumption, PCA = Patient Controlled Analgesia, *($p<0.05$)

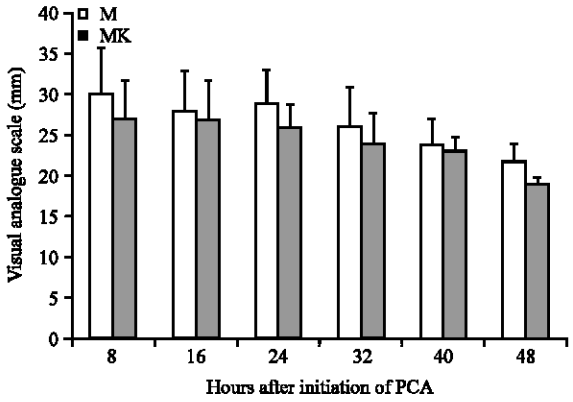

Fig. 2: Visual analogue scale score at rest during the use of PCA, PCA = Patient Controlled Analgesia

The need for rescue analgesia was more frequent in morphine group (10 patients: 25%) compared with morphine ketamine group (only 2 patients: 5%) ($p< 0.05$). Haemodynamic data, respiratory rate and pulse oximetry are shown in Table 3. These variables were comparable in the two groups except that respiratory rate was significantly lower in the morphine group 32 h after initiation of PCA :12.3 (3.2) vs. 16.8 (2.1) ($p<0.05$).

Also SPO_2 showed significantly lower values in the morphine group: 93.1 (2.3) vs. 96.3 (2.1) ($p< 0.05$). Arterial blood gases are shown in Table 4. Values were comparable in both groups except that PaO_2 was significantly lower in morphine group 32 h after initiation of PCA: 91 (7.2) vs. 98.2 (3.1) ($p<0.05$).

Comparing preoperative values, FVC and FEV1 showed significant reduction in both groups. Furthermore, they showed a significant difference between groups with a greater decrease in the morphine group 24 h and 48 h after initiation of PCA (Fig. 4, 5).

FVC at 24 h was 46% (8) in morphine group vs. 62% (9) in morphine ketamine group ($p<0.05$). At 48 h it was 58% (7) vs. 77% (11) ($p<0.05$).

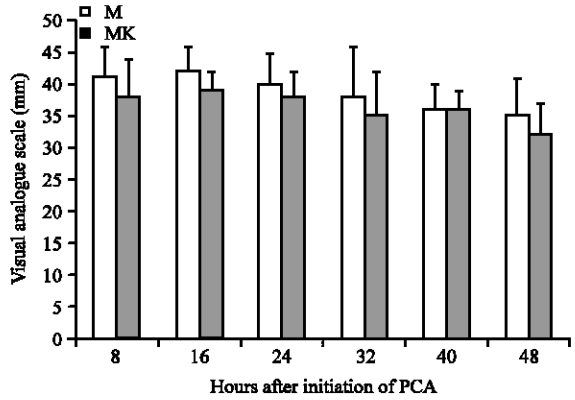

Fig. 3: Visual analogue scale score at mobilization during the use of PCA, PCA = Patient Controlled Analgesia

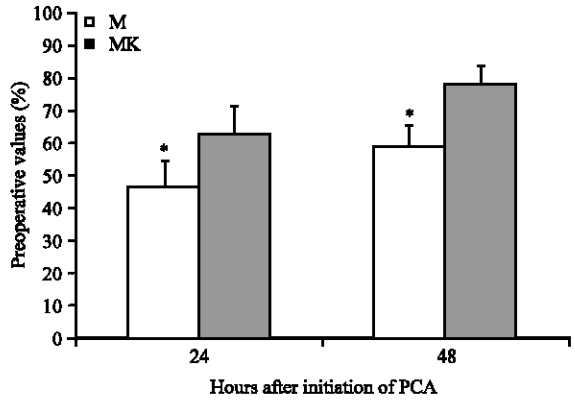

Fig. 4: FVC in both groups expressed as a percentage of the preoperative values. Data are mean (SD), PCA = Patient controlled analgesia, *($p<0.05$) compared with the preoperative value

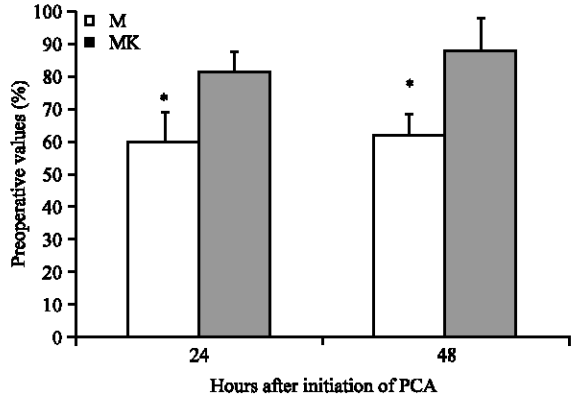

Fig. 5: FEV1 in both groups expressed as a percentage of the preoperative values, Data are mean (SD), PCA = Patient controlled analgesia, *($p<0.05$) compared with the preoperative value

Table 5: Incidence of complications in the two groups

Complications in both group	Morphine group	Morphine ketamine group
Nausea	8*	*2
Pruritis	1	1
Hallucination	1	1
Dreams	1	1
Blurred vision	-	-
Agitation	1	1
Oral secretion	2	3
Episodes of desaturation (<90%)	12*	*5

* $p<0.05$

FEV1 was 60% (9)vs. 81% (7) at 24 h ($p<0.05$). At 48 h it was 62% (6) vs. 87% (11)($p<0.05$).

Ramsay score showed no difference between the two groups and was maintained between 2 and 3 during the study.

The incidence of side effects was comparable in the two groups expect for nausea and desaturation (Table 5). Incidence of nausea was significantly higher in morphine group than morphine ketamine group (8 vs 2) ($p<0.05$). Episodes of desaturation (<90%) were significantly more frequent in morphine group (12 vs 5) ($p<0.05$). Incidence of other side effects (puritis, hallucinations, dreams, blurred vision and oral secretion) were comparable in the two groups.

Regarding patient satisfaction, it was significantly higher in morphine ketamine group than in morphine group (87.5 vs 32.5%) ($p<0.05$).

DISCUSSION

This prospective double blinded randomized study confirmed the primary hypothesis that adding small doses of ketamine to morphine for PCA allowed a significant reduction in cumulative morphine consumption associated with better post operative analgesia respiratory functions and patients satisfaction

Several studies have reported a benefit of ketamine use with no difference for cognitive adverse events and lower cumulative analgesic doses for quite better analgesic control (Guillou *et al*., 2003; Michelet *et al*., 2007; Adriaenssens *et al*., 1999). Many factors may account for these beneficial effects. Morbidly obese patients undergoing upper abdominal surgery admitted to SICU experience prolonged noxious stimuli caused by the inflammation reaction of damaged tissues and also created by the monitoring environment, therapeutic devices and nursing care (Guillou *et al*., 2003). In this context, central sensitization to pain may take place despite the use of adequate doses of opioids.

In addition to inhibition of sensitization in nociceptive pathways, prevention of opiate mediated activation of pronociceptive systems and opiate tolerance may be another mechanism of pain prevention by

ketamine (Himmelseher and Durieux, 2005). The development of rapid tolerance and delayed hyperalgesia after intraoperative and postoperative use of different opioids has been reported in surgical patients (Chia *et al*., 1999; Guignard *et al*., 2000; Weinbroum, 2003).

In this study, ketamine has been used only for the postoperative period without pre or intra-operative administration. Although there is growing evidence that adjunction of ketamine to general anesthesia with a preemptive effect is beneficial in a variety of surgical procedures (Himmelseher and Durieux, 2005; Bell *et al*., 2005). This study focused on the postoperative analgesic effect to allow discrimination between a sparing effect on perioperative and postoperative opioid consumption with a specific assessment of influence of ketamine on use of PCA device.

The protocol of the present study included a small dose of ketamine. This choice was supported by the comparison between the studies using ketamine in PCA devices, which indicated that there was no increased morphine sparing effect by increasing ketamine dose to 25-30 mg day^{-1} (Bell *et al*., 2005).

As recently highlighted in reviews and studies focusing on selected patients who traditionally require large doses of opioids, the adjunction of morphine in this specific population allowed a decrease in post-operative morphine consumption (Guillou *et al*., 2003; Ptrenko *et al*., 2003; Michelet *et al*., 2007).

However, conflicting results still exist concerning the potential benefit of adding ketamine to morphine for PAC. Indeed, whereas many studies agree with our result (Guillou *et al*., 2003; Adriaenssens *et al*., 1999; Lahtinen *et al*., 2004; Javery *et al*., 1996). others have failed to confirm them (Reeves *et al*., 2001).

These discripancies could be explained by differences in methodologies between studies. The lack of sparing effect and adverse cognitive effects reported by Reeves and colleagues could be related to the absence of rescue analgesia and the consecutive higher doses of morphine and ketamine required.

Morbidly obese patients are potentially suffering from restrictive pulmonary dysfunction. Upper abdominal surgery adds to their suffering (Postlethwait and Johnson, 1972). So, it was highly indicated to search for an analgesic regimen that relief their pain without further encroachment on their pulmonary functions.

Although arterial blood gases analysis revealed only limited variation between the study groups, spirometric data confirmed the hypothesis of opioid dependant depression of respiratory function.

This was evident by significantly more reduction in FVC and FEV1 in morphine group 24 and 48 h after PCA when compared with pre-operative values.

This reduction was less marked in morphine ketamine group which expressed significantly higher values than morphine group.

Previous study by Michelet *et al*. (2007) supported present results. They demonstrated significantly better spirometric data in patients undergoing thoracotomy receiving ketamine with morphine PCA than those receiving morphine PCA

Previous studies reported that even more powerful analgesic techniques such as epidural analgesia did not result in improved respiratory mechanics (Boissen *et al*., 2001).

Since high doses of ketamine could be responsible for ventilatory depressive effect (Mildh *et al*., 1998), it seems that the beneficial effect of ketamine on respiratory function is not related mainly to the influence on respiratory mechanics but it could be due to opioid sparing effect. An objective of this study was to determine whether ketamine could reduce the side effects of opioids particularly nausea.

This study demonstrated significantly lower incidence of nausea. This finding is supported by previous reports which reported similar effects (Bell *et al*., 2005).

Being administered in small doses, ketamine infusion was not associated with psychomimetic effects or cognitive impairment.

CONCLUSIONS

Adding small doses of ketamine to morphine in PCA devices appears to be an alternative strategy for limitation of postoperative respiratory disorders and for pain control when an intravenous analgesia is scheduled after upper abdominal surgery in morbidly obese patients. Future clinical trials should focus on high risk groups for opioid resistant acute postoperative pain e.g. chronic therapeutic opioid intake, substance abusers and amputations.

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