

POST-OPERATIVE ANALGESIA IN PATIENTS UNDERGOING MAJOR SURGERIES: EFFECT OF ADDING IV KETAMINE TO MORPHINE IN PRESENCE OF MORPHINE RESISTANT PAINBlessy Mathew¹, Arti Rajkumar², Lalita Afzal³, Mary Verghese⁴, Narjeet Kaur⁵**HOW TO CITE THIS ARTICLE:**

Blessy Mathew, Arti Rajkumar, Lalita Afzal, Mary Verghese, Narjeet Kaur. "Post-Operative Analgesia in Patients Undergoing Major Surgeries: Effect of Adding IV Ketamine to Morphine in Presence of Morphine Resistant Pain". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 21, May 26; Page: 5717-5726, DOI: 10.14260/jemds/2014/2655

ABSTRACT: Peri-operative management of opioid resistant pain is major clinical problem especially in the immediate postoperative period. The role of NMDA receptor in the processing of nociceptive input has lead naturally to renewed clinical interest in NMDA receptor antagonist such as ketamine. This paper reviews the use and efficacy of adding low dose ketamine to morphine in management of acute post-operative pain in patients who perceive pain in spite of large consumption of morphine and added advantages of decreasing opioid consumption and there by resulting in minimizing dose related side effects. We conducted a randomized double blind study on 120 patients undergoing major abdominal surgery. All patients were kept in PACU post operatively and were given basal analgesia with IV morphine till maximum of 100µg /kg within 30 min period, but if patient still complained of pain (≥ 6 of 10 on VAS) with an acceptable cognition state (≥ 15 in the MMSE) and who rated themselves not sedated (≥ 5 of 10 on VAS) were taken as resistant to morphine and were enrolled in one of the two treatment groups. The MS group received 3 boluses of 30 µg/kg of morphine plus saline whereas MK group received 3 boluses of 15 µg of morphine plus 250 µg/kg of ketamine. The total dose of morphine required by MK patients (0.42 ± 0.12 mg/kg) was significantly less than MS patients (1.21 ± 0.43 mg/kg). ($P < 0.0001$). The quality of analgesia was in favor of MK group even in terms of rescue analgesia as amount of diclofenac required was double in MS patients than in MK patients. (186.84 ± 37.83 vs. 83.57 ± 30.28 , $P = 0.0001$). The VAS score at rest and ambulation was significantly less in MK group as compared to MS group at 180 minutes ($P < 0.001$). The 10 minute level of wakefulness (1-10 VAS) in the MS group (6.88 ± 1.09) was significantly ($P < 0.0001$) less than MK group (8.28 ± 0.43). Postoperative nausea and vomiting was seen in 68.37% of MS patients as compared to only 8.30% of MK patients ($P = 0.0001$). No hemodynamic ill effects or psychosomatic effects were seen in MK group. We concluded that the postoperative administration of concomitant small doses of MK provided rapid and sustained improvement in pain control in major abdominal surgeries.

KEYWORDS: Analgesia, Post-operative, Morphine, Ketamine.

INTRODUCTION: Acute postoperative pain relief is one area still quite inadequately managed. Adequate postoperative analgesia improve the total surgical outcome especially after abdominal surgeries in terms of pulmonary function by preventing pain induced diaphragmatic splinting and thereby hyperventilation,¹ more rapid return of gastric emptying earlier bowel movements and lesser nausea and vomiting.²

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The common occurrence of surgical patients perceiving pain intensively, despite the postoperative administration of ample amounts of IV morphine, suggests a failure of sustained effectiveness. Large opioid doses were shown to be hazardous to the awakening patient because of potential respiratory and hemodynamic depression. Supplementations with rescue analgesics (NSAIDs) can compensate for unsatisfactory effect of primary antinociceptive drug, but they too might evoke adverse effects.

There is evidence to suggest that the lack of effectiveness of postoperatively administered morphine is due to the activation of NMDA (N-methyl-D-aspartate) receptor³. If not effectively inhibited in time, the process may evoke into a complex change in neural plasticity, resulting in central sensitization and severe pain.

Strong pain stimuli such as surgical incision can activate N-methyl-D-aspartate receptors and produce hyperexcitability of dorsal root neurons. This included central sensitization, wind up phenomena and pain memory. Ketamine, a nociceptive antagonist of NMDA receptors, can prevent the induction of central sensitization caused by stimulation of peripheral nociception as well as blocking the wind-up phenomenon.⁴

It has been reported that μ receptors activation by opioids also leads to a sustained increase in glutamate synaptic effectiveness at the level of NMDA receptor leading to its activation³. This scientific background could be the explanation for clinical observation that when an opioids is used alone in large doses for a prolonged period, it may induce tolerance via on NMDA activation which can lead to increased postoperative pain.

Ketamine, a non-competitive antagonist of NMDA receptor can prevent the induction of central sensitization caused by stimulation of peripheral nociceptor as well as helps in blocking the wind-up phenomena.⁵ Ketamine by blocking these NMDA receptors can prevent the development of tolerance.

This suggests that a 'balanced analgesia' with ketamine could be fruitful strategy to prevent pain sensitization induced by both nociceptive surgical inputs and opioids. Pathophysiological studies of spinal cord hyperexcitability via activation of NMDA receptors strongly suggest that concomitant administration of NMDA antagonist such as Ketamine and opioids may be advantageous.⁶

It has been postulated that the dose in which ketamine has no analgesic potency on its own but when used in combination with an opioid, yields on opioid sparing effect and superior pain relief than either drug alone⁷ and in this range ketamine does not appears to have any hemodynamic or respiratory depression, sedation or psychomimetic effect.⁸

MATERIALS & METHODS: After ethic committee approval, a double blind randomized study was conducted on 120 patients of either sex and age of 20-70 years undergoing major abdominal surgeries. Exclusion criteria included long term use of opioid medication or substance obese, chronic pain, morbid obesity, psychiatric disease, respiratory disease in acute phase.

All patients were pre-medicated with T. Diazepam 0.2 mg/kg night before and on morning of surgery. General anesthesia was administered by I/V Sodium Thiopentone 4-5 mg/kg, Suxamethonium 2 mg/kg IV was given to facilitate tracheal intubation. Vecuronium/Atracurium was used to obtain muscle relaxation, fentanyl 1.5-2 μ g/kg for intraoperative analgesia and Nitrous oxide/ oxygen (60:40) enriched with halothane/isoflurane to maintain anesthesia. At the end of surgery, residual neuromuscular blockade was antagonized with IV neostigmine and glycopyrrolate.

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Patients were extubated as soon as they opened their eyes to verbal commands and had optimal respiration. No regional anesthesia was used on any of these patients.

All patients were kept in post-Anesthetic Care Unit (PACU) and received inj morphine IV 2 mg every 4-5 min until pain was relieved.

1. Subjective pain intensity was graded on self-rating VAS graded as 'no pain =0 and worst pain = 10'.
2. Subjective pain intensity on deep breathing was graded as 'no pain =0 and worst possible pain = 10'
3. Subjective level of wakefulness was assessed by self-rated VAS from '1= heavily sedated' to 10= fully awake'
4. Subjective feeling of well-being – VAS of 1= sad and gloomy to 10 = happy and content.

These patients were included in this study who had received 100 µg/kg of morphine within 25-30 min period but still complained of pain (≥ 6 of 10 on VAS) whom the attending physician found in acceptable cognitive state (≥ 15 in MMSE) min-initial state examination or who rated themselves not sedated (≥ 5 of 10 on VAS), all these patients were randomly enrolled into one of the 2 treatment protocols.

Group I (MS Group) – received 3 bolus of 30µg/kg of morphine plus saline over 10 min or till VAS <4.

Group II (MK Group) – received 3 boluses of 15µg/kg of morphine plus 250 µg/kg of ketamine over 10 min or till VAS <4.

If pain was not attenuated with either regime, a rescue dose of IM diclofenac 75 mg was given. Before starting treatment patient's cognitive state was evaluated by using MMSE (from 0 to 30) or sedation scale. VAS score were assessed every 5 min for 1st hour and every 15 min afterwards.

Vital signs included non-invasive BP, heart rate, respiratory rate, O₂ saturation were recorded at half hourly interval. Untoward side effects (nausea, vomiting or any distress) were also recorded.

All physiological variables during the observation periods in PACU were analyzed with student't' test. All values were expressed as mean \pm SD, with significance defined as $p \leq 0.05$.

RESULTS: Both the groups, MS and MK were comparable with respect to age, sex ASA grading and duration of surgery (Table 1).

The amount of analgesics that was requested by the patients to alleviate pain was found to be associated with the drug regimes. It was significantly ($p < 0.0001$) less for MK compared with MS subjects (Table 2); MS patients received almost twofold the number of injections i.e. boluses of the drug as compared to MK group and difference was significant ($P = 0.0001$) (Table 2).

Furthermore patients in MS group needed almost twice the amount of rescue analgesia than MK group over period of 24 hours and difference was statistically significant ($p = 0.0001$) (Table 2).

The subjectively evaluated pain intensity during the 4 hours PACU stay was significantly lower in MK group was compared with their MS counterparts ($P < 0.001$) despite the large amount of morphine administered to the MS group (Table 2). The VAS scores became significantly low immediately (within 10 min) in MK group as compared in MS group ($p = 0.001$) (Fig. 1).

Thus showing that MK group patients had faster onset of analgesia. At 210 min and 240 min both the groups had satisfactory pain relief as VAS in both groups were ≤ 4 ($p = 0.367$). Also a

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consistent decrease in VAS on coughing was observed at 0 min postoperatively to 240 min after treatment (Fig. 2) in MK group $P=0.001$).

The VAS scores on ambulation/ deep breathing were significantly lower in patients in MK group as compared to those in MS group at all timings but the difference was statistically significant from 60 – 180 min. ($P= 0.001$) suggesting that patients in MK groups had superior analgesia (Fig 2).

The patients subjective wakefulness and feelings of well-being indicated that administration of MK was associated with better scores ($P<0.0001$) than those with MS (Fig.3).

Improvements in these two self-rated variables in the MK patients continued overtime indicating an overall ($p<0.001$ and $P<0.001$) better sustained effect of MK on each variable throughout the observation period compared with MS except at 210 and 240 min when the values were insignificant. ($P>0.5$ and $P>0.042$).

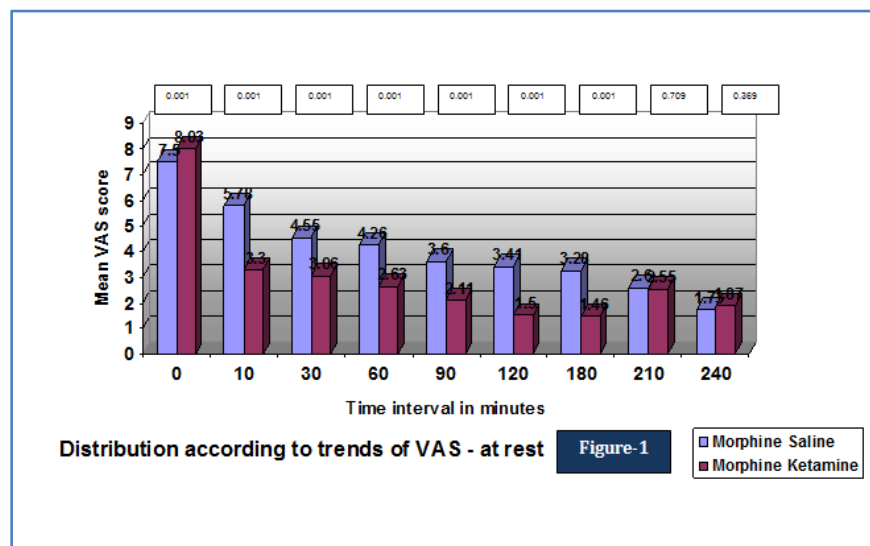
MMSE scores at 30 mints after injections were much better in MK than in MS patients. The MS group had significantly more incidence of PONV ($P<0.0001$) than MK group (Fig.4). 41 incidences (at rate of 68.37%) of postoperative PONV were recorded among MS patients in PACU, compared with 5 (8.3%) among MK group. No other side effects were seen in any patients of either groups.

	Age (yrs.) Mean \pm SD	Sex (Mean %)		ASA Mean%		Duration of surgery Mean \pm SD
		Male	Female	I	II	
MS	45.97 \pm 11	63.33	36.67	50	50	2.27 \pm 0.16
MK	40.57 \pm 12.80	63.33	36.67	40	60	2.28 \pm 0.57

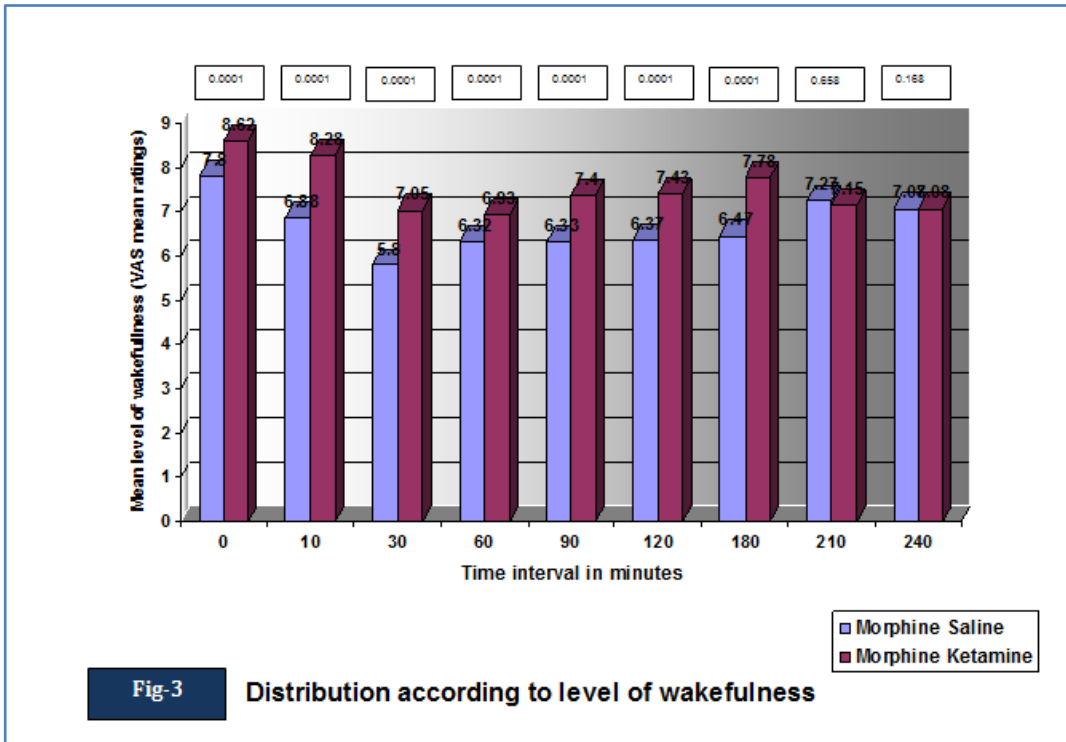
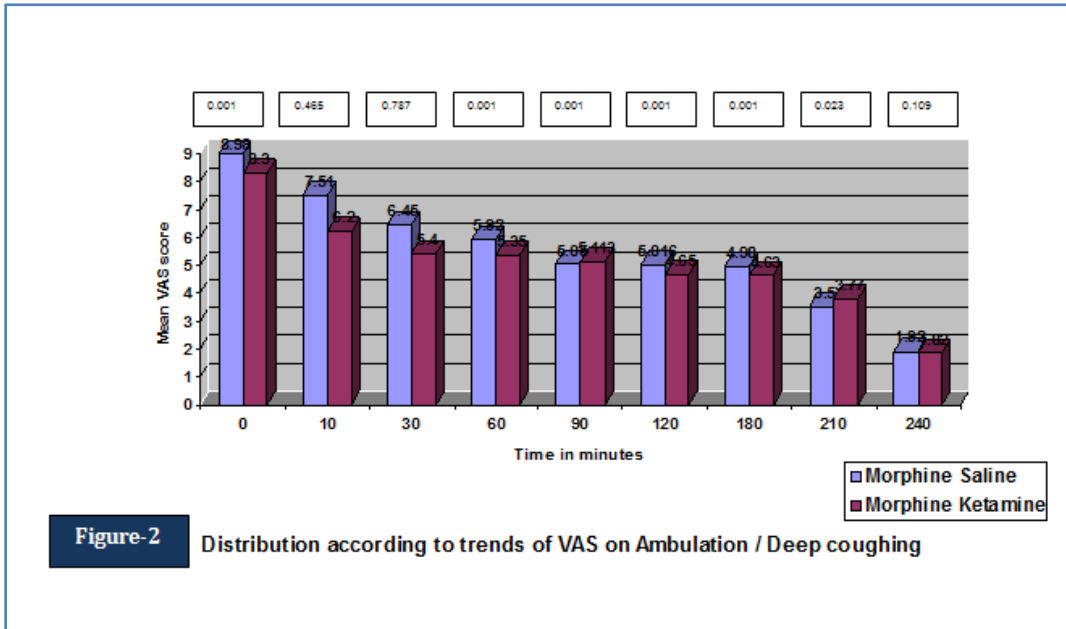
Table 1

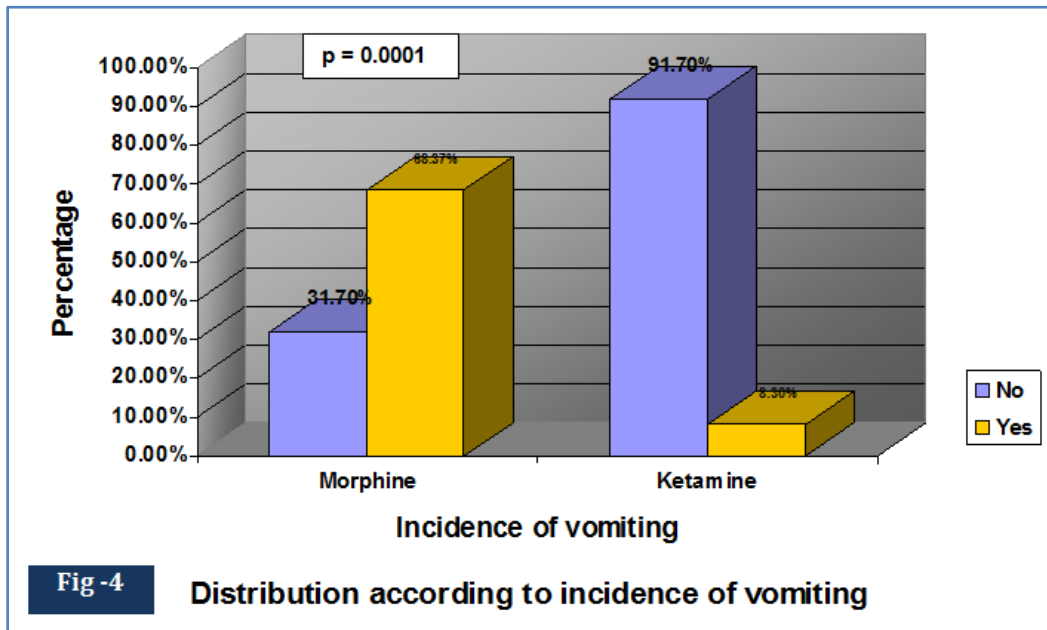
Drug	MS Mean \pm SD	MK Mean \pm SD	P-value
No. of doses	2.49 \pm 0.504	1.11 \pm 0.404	0.0001
Total consumption of morphine (mg/kg)	1.21 \pm 0.43	0.42 \pm 0.12	0.0001
Total amount of rescue drug in 24 hrs.	186.84 \pm 37.83	83.57 \pm 30.25	0.0001

Table 2



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DISCUSSION: After the approval from hospital ethics committee this comparative study was conducted on 120 patients to evaluate postoperative analgesic effects of adding IV ketamine to morphine in presence of morphine resistant pain. We found that IV administration of a combined dose of MK promptly and satisfactorily resolved pain that had been unresponsive to IV morphine. Pain at rest was significantly lower in MK groups for first 180 minutes and had quicker onset of analgesia, as VAS- at rest became significantly lower at 10 min after drug administration as compared to 60 min in MS group patient.

Thus we concluded that small doses of MK ($p=0.001$) provided rapid and sustained improvement in pain control, better than morphine alone. The analgesic efficacy of VAS-on movement and coughing was also found superior for MK group as compared to MS group patients for most of the study period.

MS patients received almost two fold the number of injections i.e. boluses of morphine as compared to MK group ($p<0.0001$) and even the diclofenac doses for rescue analgesia required in MS patients was two-fold as compared to MS patients (186 ± 37.83 vs. 83.57 ± 30.25). Forty one of 60 patients in MS group had incidence of PONV as compared to five out of 60 in MK group ($P<0.0001$). Ketamine administration was associated with an immediate increase in SPO_2 in first 10 mins leading to better respiration in MK group with greater self-rated level of wakefulness and no ketamine associated psychomimetic effects.

If given alone, ketamine at small doses ($<250 \mu\text{g}/\text{kg}$ i/v) as given in this study might produce, subanalgesia that would last only a few minutes after the injection. The plasma half-life of intravenous ketamine is approximately 15 minutes, but the analgesic effect of MK in our study was clearly evident throughout the 180 minutes observation period. The dose and the drug combination given in this study allowed for the rapid and sustained improvement in postoperative analgesia.

Researchers have considered that the activated open state of NMDA receptors as produced by opioids is optimal for the effect of low dose of ketamine.⁹

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Ketamine may produce antinociception through various mechanisms of action, i.e., interaction with spinal μ receptors, NMDA receptors and activation of descending pain inhibiting monoaminergic pathways¹⁰ i.e. α_2 adrenoceptors at spinal level, however the affinity of ketamine for NMDA receptors is several folds higher than for the other two receptors, thus suggesting that small doses of ketamine as used in our study could interact more selectively with NMDA receptors and explain its effective antinociception.¹¹⁻¹⁴

Nevertheless while morphine and other opioids produce μ receptors agonist action and activation of monoaminergic descending pathways at the spinal level,⁸ they also activate NMDA receptors resulting in hyperalgesia and development of tolerance to opioids.

Acute tolerance may even occur after a single opioid administration.^{15,16} Animal and clinical studies demonstrate that acute opioid tolerance can be prevented by co administration of NMDA receptor antagonist^{9,17} as shown in our study by adding just 250 $\mu\text{g}/\text{kg}$ of ketamine to 15 $\mu\text{g}/\text{kg}$ of morphine in postoperative patients. Weinbroum et al (2003)¹⁷ found that subjectively evaluated pain intensity during the 2 hour PACU stay was significantly lower for MK patients as compared to their MS counterparts despite large amounts of morphine administered.

The IV administration of combined small doses of MK promptly and satisfactorily resolved pain that had been unresponsive to IV morphine. There was an immediate (<10 min) significant ($p<0.0001$) decline in pain intensity in MK group patients. Thomas Edrich et al 2004¹⁸ reported a burn case in which ketamine was successfully used for long term analgesia and sedation in patients who had developed tolerance to opioids.

There is evidence to suggest that lack of effectiveness of postoperative morphine is due to activation of NMDA receptors. If not inhibited well in time, the process may evolve into complex changes in neural plasticity resulting in central sensitization and severe pain. There is also evidence that surgery and opioid share NMDA receptor activation, therefore adequate blockade of these receptors by ketamine as an adjuvant to opioids might benefit the patients by evoking attenuation of pain, secondary hyperalgesia and opioid sparing effects.⁸

This would suggest that small doses of ketamine interact more selectively with NMDA receptors. Adding of low dose of ketamine before surgical stimulation (Preemptively)^{11,19} and perioperatively¹⁷ as shown in our study which standardized use of morphine for postoperative analgesia resulted in significantly improved analgesia as VAS scores were found to be significantly low. VAS at rest ($P<0.001$), ambulation, deep breathing and coughing ($p<0.001$) were significantly low in MK group than MS group in first 3 hours leading to better feeling of well-being in MK patients ($P<0.0001$) resulting in early ambulation and recovery.

Thus suggesting, that improved pain relief by a combination of drugs; resulted from selective block of each opiate receptors site, against different type of pain. It has been suggested that analgesics acting at different types of opiate receptors synergize and thus produce more potent analgesia than would be produced by any of analgesic alone.^{20,21}

Stubhang et al¹⁹ inferred that blockade of NMDA receptors by preemptive low doses intravenous ketamine infusion, prevents the central sensitization to pain caused by increased nociceptive inputs during and after surgery. Ketamine reduces morphine requirement and improves mobilization as suggested by different studies.^{17,22,23}

Christophe Menigaux et al 2000²² reported that there was a better knee flexion for MK group compared to MS group (47 ± 13 vs. 35 ± 10) and they commented better analgesia allowed early and

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intensive physiotherapy accelerating functional recovery after knee surgery. As requirement of morphine was less in MK group, morphine associated side effects were also less frequent in MK group as compared to MS group.^{17, 24}

Total consumption of morphine in our study was significantly low (P0.0001) in MK group as compared to MS group (0.42 ± 0.12 vs. 1.21 ± 0.43) hence reducing the incidence of side effects like PONV to negligible. Forty one patients in MS group complained of PONV as compared to only five in MK group (P<0.0001). The three fold amount of morphine consumed in MS group was most probably the causative factor. The low doses in MK group improved spO₂ level within 10 minutes whereas in MS group there was fall in saturation from 0-10 min, but change in spO₂ in both groups was not significant after 10 minutes.

This was attributed to better analgesic effect by MK group enabling the patient to breathe deeply, cough better and maintain adequate minute ventilation. Other side effects like hallucinations, unpleasant dreams, acute psychosis^{25 and 26} were not seen in our study. There was no changes in cognition, perception or mood swings in any of our patients even after 24 hours.¹⁷

In conclusion, administration of concomitant small doses of ketamine with morphine provided sustained improvement in post-operative pain in patients who had inadequate relief of pain in spite of receiving large doses of morphine. Decreased opioid consumption and improved analgesia translated into greater level of wakefulness, overall well-being and decreased incidence of opioid related side effects particularly PONV.

At small doses of ketamine that we used in our study the incidence of psychomimetic effects and cognitive impairment was found to be negligible. We suggest that administration of small dose of ketamine in adjunct to morphine may be a valuable strategy for pain management in major abdominal surgeries.

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