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# *"The Efficacy of Bolus Epidural Morphine with Ketamine as Postoperative Analgesia after Hepatic Resection: A Randomized, Controlled, Double Blind Study"*

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## ABSTRACT:

Abstract:

Background: Postoperative pain management after hepatic resection remains challenging due to the narrow therapeutic index of opioids, which limits their use due to dose-dependent adverse effects. Optimizing epidural analgesia with adjuvant agents such as ketamine may enhance pain relief while reducing opioid consumption and related side effects.

Objective: This study was conducted to evaluate the effectiveness and safety of bolus epidural morphine with ketamine compared to bolus epidural morphine when either added to bupivacaine for postoperative pain management in elective hepatic resection.

Patients and Methods: Seventy-six patients who underwent hepatic resection were randomized to receive either epidural morphine-bupivacaine (MG group) or morphine-ketamine-bupivacaine (MKG group). The primary outcome was the time to first opioid request and 24-hour postoperative morphine consumption. Secondary outcomes included associated hemodynamic variables, postoperative pain scores, and any adverse effects.

Results: Patients in Group MKG demonstrated significantly prolonged time to first analgesic request (22.58±3 vs 17.24±5 hours) and reduced 24-hour morphine consumption (3.74±1 vs 8.89±2 mg) compared to Group MG ($P<0.001$). VAS scores were significantly lower in MKG from 4-24 hours ($P<0.001$), with comparable adverse event rates between the groups ($P>0.05$).

Conclusions: Adding ketamine to epidural morphine and bupivacaine prolongs analgesia, reduces opioid requirements, and minimizes side effects, offering a superior alternative for post-hepatectomy pain management.

**Keywords:** Morphine, Ketamine, Epidural Analgesia, Postoperative pain, Hepatic resection.

**Introduction:**

Liver resection is a major surgical management used to treat both benign and malignant hepatic tumors. It is usually carried out in an open manner using a right subcostal or right inverted L-shaped incision; as a result, it is linked to severe postoperative pain [(1)].

Effective postoperative pain management is crucial for patients undergoing hepatic resection, as inadequate analgesia can impede recovery, delay mobilization, and increase the risk of complications [(1,2)]. Postoperative analgesia is still difficult in this scenario, mostly due to the traditional opioid's narrow therapeutic index [(3,4,5)].

Epidural analgesia is considered the gold standard for managing postoperative pain following major abdominal surgery, including liver resections, because it provides better pain control than systemic opioids. However, the optimal mixture of agents administered epidurally to achieve maximum analgesic efficacy and decrease undesired adverse effect remains under active investigation [(1)].

Morphine, for its potent analgesic effect and its hydrophilic properties, is one of the most widely used opioids for epidural analgesia. Morphine has a lengthy duration of action with a wide-range segmental effect [(6)]. However, its administration is linked to adverse effects including respiratory depression, pruritus, and nausea that can slow postoperative recovery. Adjunct agents such as ketamine would be considered in an effort to mitigate these negative influences and to enhance their analgesic effects. Ketamine acts as N-methyl-D-aspartate (NMDA) receptor antagonist, demonstrating clinically significant analgesic and opioid-sparing effects that have the potential to reduce postoperative opioid requirements and associated unwanted effects [(7,8)].

Combined epidural morphine with ketamine targets to benefit from the synergistic effects of both drugs. Morphine provides strong analgesia, and the NMDA receptor antagonism of ketamine can inhibit central sensitization and limit the development of opioid tolerance. Adding ketamine to an opioid-based regimen enhances analgesic efficacy and decrease opioid consumption in multiple surgical populations [(5,9)], making it particularly valuable for procedures involving significant tissue trauma like hepatic resection.

While patients exhibited normal coagulation at time of epidural placement, post-hepatectomy coagulopathy typically peaks on postoperative 2-3 days [(5)], making catheter maintenance hazardous. This justifies our choice for single-shot, low-dose epidural approach. However, evidence remains limited regarding ketamine's additive effects to epidural morphine specifically in hepatic resection patients, highlighting the need for further investigation of this optimized analgesic strategy in this high-risk

population.

**Hypothesis:**

This trial tested the hypothesis that adding ketamine to epidural morphine and bupivacaine improves analgesia while reducing complications compared to morphine alone.

**Aim of the Study:**

This study assessed the efficacy and safety of adding ketamine to an epidural morphine-bupivacaine regimen compared to morphine-bupivacaine alone for postoperative analgesia in patients undergoing elective hepatic resection.

## Patients and Methods:

### Study Design

This study was conducted as a randomized, double-blind, positive-controlled trial at the Gastro-Intestinal Surgery Center of Mansoura University between January 2021 and December 2024. The study protocol received approval from both the Institutional Review Board (IRB) of Mansoura Faculty of Medicine (Approval Code: MS.20.09.1268) and the Pan African Clinical Trial Registry (Registry Code: PACTR202506732871749). All study participants provided written informed permission before their involvement.

### PATIENTS

The study enrolled patients between 20–65 years old, of both sexes, classified as ASA physical status I–II with Child-Pugh grade A, scheduled for hepatic resection via a standard right subcostal incision. However, Exclusion criteria comprised refusal to participate, Child-Pugh grade B or C, dementia, neuromuscular disorders, coagulation or hematologic abnormalities, known allergies or contraindications to regional anesthesia or to study medications (opioids, ketamine, or local anesthetics), chronic pain conditions, opioid dependence, and a BMI $<18$ kg/m² or $>40$ kg/m².

### Randomization and Blinding

To minimize bias, participants were randomly assigned (1:1 ratio) to study groups using a computer-generated randomization sequence. A sealed opaque envelope system was used to conceal allocation, which was opened by a third-party anesthesiologist not involved in the trial. The study drug syringes were prepared by this anesthesiologist in identical volumes and appearances to maintain blinding. Throughout

the study, patients, administering anesthesiologists, and outcome assessors remained all blinded to group assignment.

**Preprocedural management**

The night before the surgery, patients were briefed about the nil per oral (NPO) guidelines as well as familiarized with the visual analogue score (VAS) of pain. On arrival to the operating theater, essential monitoring devices (electrocardiograph, noninvasive blood pressure cuff, and pulse oximeter) were applied, and baseline vital signs were documented. Two wide pore (18-G) intravenous (IV) cannulas were inserted in suitable large peripheral veins.

**Interventions and epidural protocol**

After good sterilization of the patient's back, 3 ml of local analgesia (lidocaine 1%) was injected subcutaneously at the site of puncture. A midline technique was used for the thoracic puncture at T7-T9 using an 18-G Tuohy needle with a loss of resistance technique, and no epidural catheter was inserted. Three unsuccessful attempts at needle implantation were not included. A 10 mg morphine (20 mg/1ml) was diluted in 20 ml 0.9% normal saline (NS) (1ml=1mg morphine). Both groups received 3ml of the diluted morphine in a total volume of 10ml containing 2.5ml bupivacaine (0.125%) as follows:

- **Morphine group (MG):** patients received 2.5ml of 0.5% bupivacaine, 3ml of the diluted morphine (3mg), and 4.5 ml NS 0.9% to reach the total volume of 10mL with 0.125% bupivacaine concentration (as positive control group).

- **Morphine-ketamine group (MKG):** received 2.5ml of 0.5% bupivacaine with 3ml of the diluted morphine (3mg), 0.6ml (30 mg) of ketamine (50 mg/ml), and NS (0.9%) to get the same 10ml total volume with 0.125% bupivacaine concentration.

**Anesthesia:**

In accordance with the standard institutional protocol, general anesthesia (GA) was induced and maintained using slowly IV injection of 1.5µg/kg fentanyl, propofol (2mg/kg until loss of verbal contact), and atracurium (0.5mg/kg) to facilitate proper placement of the endotracheal tube. Every patient was mechanically ventilated in volume-controlled mode with respiratory rate adjustment to keep tidal $CO_2$ between 30-40 mmHg. Anesthesia was then maintained using isoflurane (1-1.5%) in $O_2$/air mixture ($FiO_2$ 50%) with incremental dose of atracurium 0.15mg/kg.

For fluid infusions, hemodynamic monitoring, and determination of acid-base parameters, an arterial line and central venous catheter were inserted under complete aseptic precautions. Following surgery, any remaining neuromuscular blockade was reversed. Patients who met the extubation requirements were

extubated, moved to the post-anesthesia care unit until they met the Modified Aldert Score of 9. Every patient spent at least 24 hours in the intensive care unit. Postoperatively, all patients will receive standard analgesia (paracetamol 1 gm IV every 6 hours which started 30 minutes before finishing the surgery ± rescue IV analgesic as per VAS score).

One hour following surgery, pain perception was evaluated using VAS. Patients were asked to circle the number from 0 to 10 as per their response to pain. Zero indicates no pain, whereas 10 points to the worst pain ever possible. Rescue IV morphine (3 mg boluses) was given as needed if VAS recorded ≥4, with incremental doses permitted up to a maximum of 0.1 mg/kg/4 hours if pain persisted.

Hypotension was treated with IV fluids and 5 mg ephedrine (IV) boluses if the systolic blood pressure (SBP) was less than 90 mmHg or >25% reduction in mean arterial blood pressure (MAP). Bradycardia (HR≤50 bpm) received atropine (0.5mg IV), while tachycardia (HR>100 bpm) or hypertension triggered by inadequate analgesia was managed with fentanyl (50µg IV), such cases were subsequently excluded from the study.

**Outcomes measures**

The primary outcomes were the time to first opioid request and 24-hour cumulative morphine consumption. Secondary outcomes involved surgical duration and hemodynamic parameters (HR and MAP), monitored preoperatively, immediately after induction, every 15 minutes intraoperatively, and postoperatively at 30 minutes, 2, 4, 6, 12, and 24 hours.

Additionally, the postoperative pain scale was assessed according to VAS at 1, 2, 4, 6, 12, and 24 hrs. Any unwanted side effects, either opioid- or ketamine-related were also recorded postoperatively, including nausea and vomiting (PONV), pruritus, respiratory depression, or psychomimetic effects (hallucinations or dysphoria). Continuous hemodynamic monitoring (CVP and arterial pressure) was maintained intraoperatively, along with assessment of fluid, blood product transfusions, and arterial blood gas analyses.

**Sample size calculation:**

For sample size calculation, a pilot study was carried out on 12 patients showing the mean analgesia duration, as a primary outcome, of 12.90±2.43hours (morphine alone) versus 21.65±3.20hours (morphine-ketamine). Using G*Power 3.1.9.7 (2020), 34 participants per group were required to achieve 80% statistical power with a 5% significance level. Accounting for a 10% anticipated dropout rate while maintaining equal group allocation, the final enrollment target was set at 76 participants (38 per group).

**Statistical analysis:**

Data analysis was conducted using Statistical Package for Social Sciences (SPSS) program version 22.

The Shapiro-Wilk test was applied only to significant data, which suggests nonparametric data. For comparisons of numerical variables between groups, the unpaired Student t-test was used if assumptions were satisfied; otherwise, the Mann-Whitney test was used. Quantitative data were characterized by mean ± standard deviation (SD) or median, (range), while qualitative variables were characterized by frequency and percentage. For qualitative data, the Chi-square test or Fisher's exact test was used. Statistical significance was set at $p<0.05$ with the 95% confidence level.

**Results:**

This double-blind randomized study assessed 91 patients for eligibility, with 76 meeting inclusion criteria and completing the trial (15 were excluded). Participants were randomly allocated in equal numbers to either the MG or MKG group **(Fig. 1)**. Demographic and clinical characteristics including age, gender, BMI, ASA score, and surgical duration showed comparable baseline measurements between the groups **(Table 1)**.

Hemodynamic parameters demonstrated no significant intergroup differences at most timepoints, except in the MKG group for significantly lower HR between 6 and 24 hours postoperatively ($P<0.05$, **Fig. 2**) and significantly lower MAP during 60-150 minutes intraoperatively ($P<0.05$, **Fig. 3**). Spo2 showed no significant intergroup differences throughout the study times **(Fig. 4)**.

The MKG group demonstrated significantly delayed first morphine request (22.58±3 vs 17.24±5 hours, $P<0.001$) and consequently reduced total consumption (3.74±1 vs 8.89±2 mg, $P<0.001$) compared to the MG group **(Table 2)**.

Postoperative VAS was significantly lower in the MKG group from the 4th hour onward in comparison with group MG (median values, $P<0.001$), with no intergroup differences at other time-points **(Table 3)**.

The two groups showed no significant differences in postoperative hospital stay duration, PONV incidence, or other adverse effects (pruritus, respiratory depression, or psychomimetic effects) throughout the study period (all $P>0.05$) **(Table 4)**.

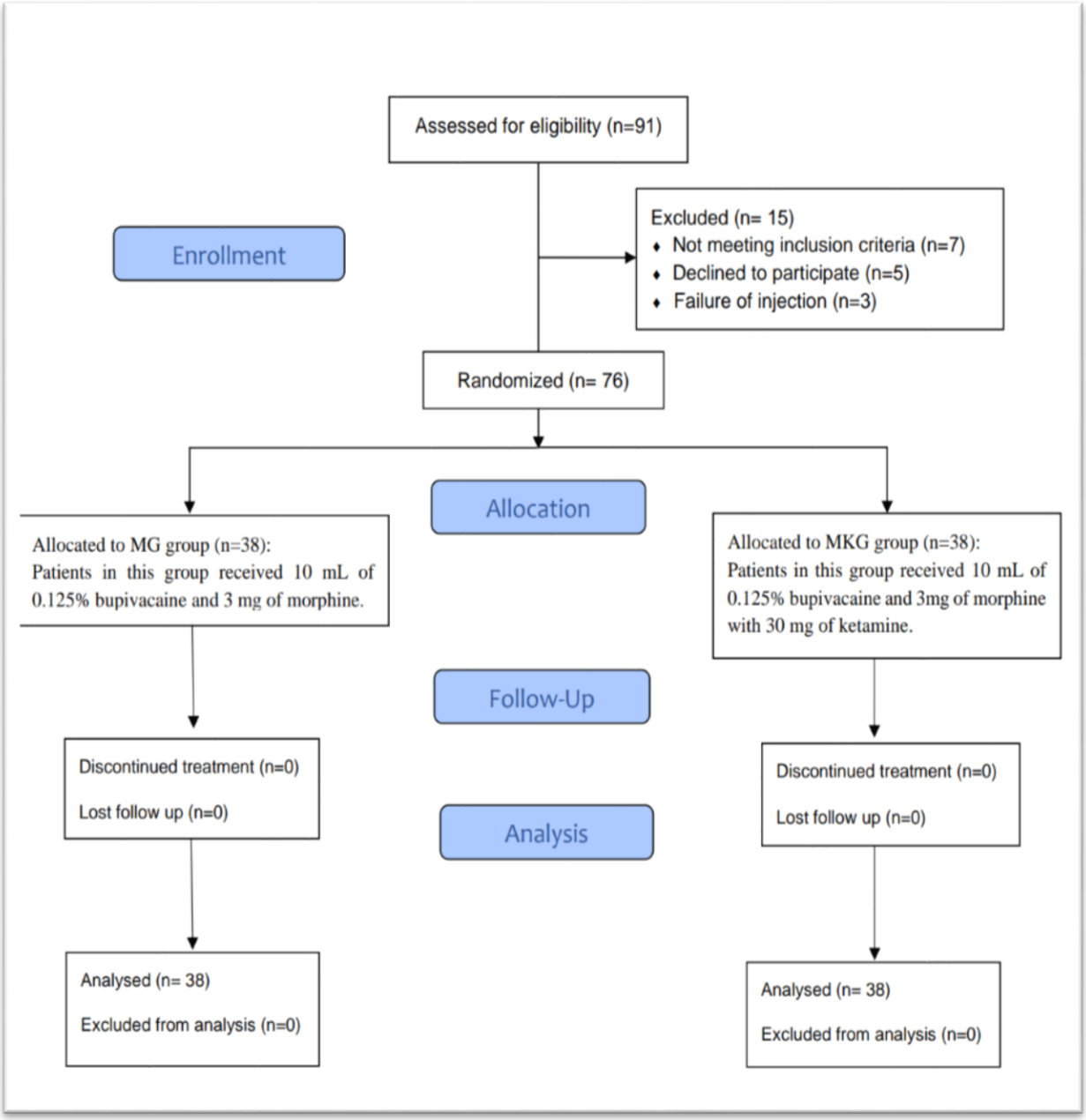


**Figure 1. Consolidated standards of reporting trials (CONSORT) flowchart**

**Table (1): Patient characteristics and operative time in the two studied groups:**

| Variables | MG group (n= 38) | MKG group (n= 38) | P-value |
|---|---|---|---|
| **Age (years)** | 56.18 ± 7 | 55.55 ± 7 | 0.686 |
| **Gender**<br>**Male**<br>**Female** | <br>25 (65.8%)<br>13 (34.2%) | <br>22 (57.9%)<br>16 (42.1%) | 0.408 |
| **BMI (Kg/m2)** | 27.54 ± 3 | 27.14 ± 3 | 0.530 |
| **ASA**<br>**I**<br>**II** | <br>14 (36.8%)<br>24 (63.2%) | <br>17 (44.7%)<br>21 (55.3%) | 0.484 |
| **Operative time (minutes)** | 173±30 | 171±21 | 0.639 |

Qualitative data are expressed as number (percent) and Quantitative data is expressed as mean±SD. **MG**: morphine-bupivacaine group. **MKG**: morphine-ketamine-bupivacaine group. **BMI**: body mass index. **ASA**: American Society of Anesthesiologists

**Table (2): Postoperative analgesia in the two studied groups**

| Variables | MG group (n= 38) | MKG group (n= 38) | P-value |
|---|---|---|---|
| **Time of first analgesic request [Duration of analgesia] (hour)** | 17.24 ± 5 | 22.58 ± 3 | <0.001* |
| **Total analgesia (morphine) (mg)** | 8.89 ± 2 | 3.74 ± 1 | < 0.001* |

Quantitative data is expressed as mean ±SD * P value is significant when <0.05. **MG**: morphine-bupivacaine group. **MKG**: morphine-ketamine-bupivacaine group. **Mg**: Milligrams

**Table (3): Analysis of VAS score in the studied groups throughout the study**

| VAS score | MG group (n= 38) | MKG group (n= 38) | P-value |
|---|---|---|---|
| **1 hours** | 0 (0-1) | 1 (0-1) | 0.111 |
| **2 hours** | 1 (1-2) | 2 (1-2) | 0.494 |
| **4 hours** | 3 (2-5) | 1 (1-2) | **<0.001*** |
| **6 hours** | 5 (2-5) | 3 (2-3) | **< 0.001*** |
| **12 hours** | 4 (1-5) | 1 (1-2) | **< 0.001*** |
| **24 hours** | 3 (2-4) | 2 (1-2) | **< 0.001*** |

Quantitative data is expressed as median (Range) *: P value is significant when <0.05. **MG**: morphine-bupivacaine group. **MKG**: morphine-ketamine-bupivacaine group. **VAS**: Visual Analog Scale.

**Table (4): Analysis of the postoperative follow up of the studied groups**

| Postoperative complications | MG group (n= 38) | MKG group (n= 38) | P-value |
|---|---|---|---|
| **Length of Stay (Days)** | 5 (4-7) | 5 (4-7) | 0.792 |
| **Nausea & Vomiting** | 9 (23.7%) | 5 (13.2%) | 0.237 |
| **Pruritus** | 0 (0%) | 0 (0%) | |
| **Respiratory depression** | 0 (0%) | 0 (0%) | |
| **Psychomimetic effect** | 0 (0%) | 0 (0%) | |

Qualitative data are expressed as number (percent). Quantitative data is expressed as median (Range). *: P value is significant when <0.05. **MG**: morphine-bupivacaine group. **MKG**: morphine-ketamine-bupivacaine group.

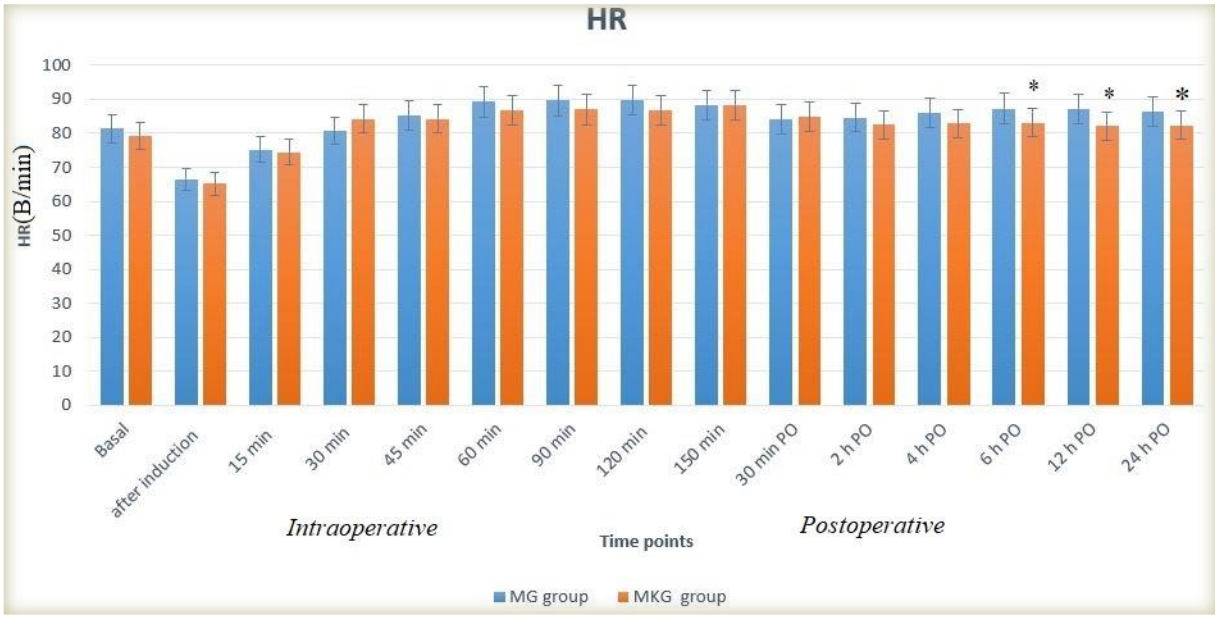


**Figure 2: HR:** Heart rate (beat/min). *: P value is significant when <0.05. **MG**: morphine-bupivacaine group. **MKG**: morphine-ketamine-bupivacaine group.

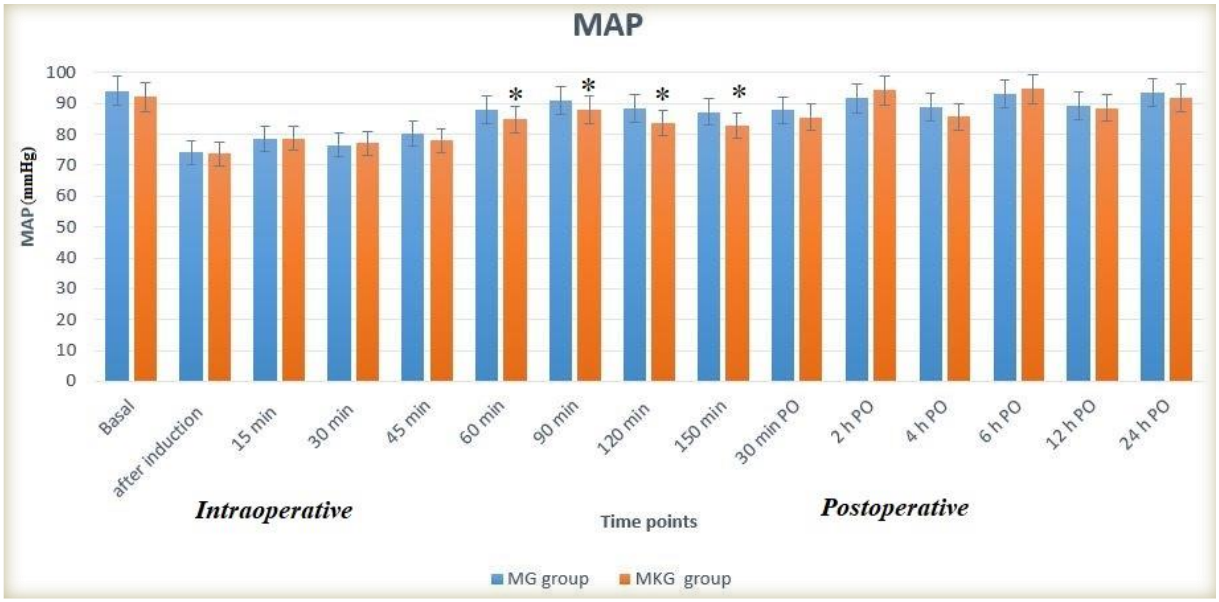


**Figure 3: MAP:** Mean Arterial Pressure (mmHg). *: P value is significant when <0.05. **MG**: morphine-bupivacaine group. **MKG**: morphine-ketamine-bupivacaine group

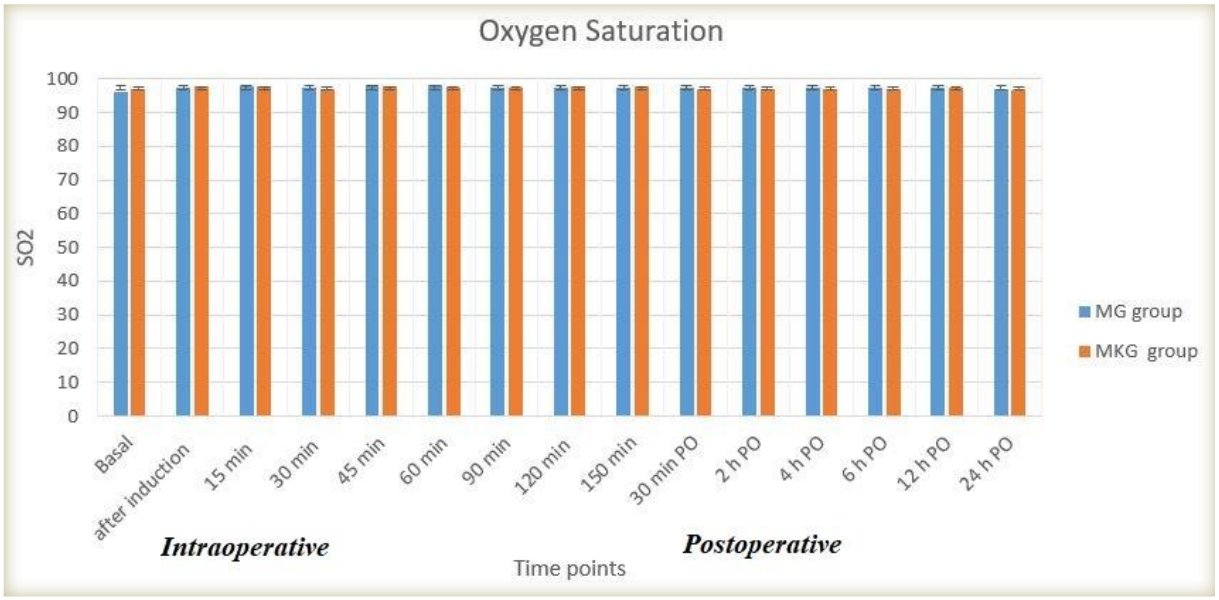


**Figure 4:** Peripheral Oxygen Saturation ($Spo_2$). **MG**: morphine-bupivacaine group. **MKG**: morphine-ketamine-bupivacaine group.

## Discussion:

Postoperative pain following open hepatic resection is particularly severe and multifactorial due to combined somatic (subcostal incision, rib retraction) and visceral (diaphragmatic irritation, hepatic capsule distension) components [10,11]**.** Current analgesic regimens fail to provide adequate pain control in 55-80% of major abdominal surgery patients [10,12], highlighting the need for more effective multimodal approaches tailored to this complex pain pathophysiology.

Posthepatectomy liver dysfunction creates a narrow therapeutic window for analgesia and impairs clotting factor production for several days (even with normal preoperative coagulation). This elevates the risk of spinal hematoma from indwelling epidural catheters**,** justifying our single-shot, low-dose epidural approach utilizing the synergistic morphine-ketamine combination. This strategy balances effective analgesia with minimized bleeding risk during the critical postoperative period [5]**.**

This randomized, positive-controlled, double-blind trial evaluated the analgesic efficacy and safety profile of adding low-dose ketamine to epidural morphine-bupivacaine for postoperative pain management in patients undergoing elective hepatic resection. The present study demonstrated significantly improved analgesia, evidenced by delayed opioid request, reduced consumption, and lower VAS scores after hepatic resection with the epidural morphine-ketamine combination. The observed 31% increase in time to first opioid request in MKG (from 17 to 22 hour) against MG group aligns with **Taurá et al.** [5] who

reported a 66% prolongation (from 27.2 to 16.4 hours) using a similar regimen in cirrhotic patients. This synergy likely stems from ketamine's NMDA receptor antagonism which alleviates central sensitization, hyperalgesia, and wind-up pain, complementing morphine's μ-opioid receptor agonism as discussed by [13].

Moreover, the enhanced analgesia observed with epidural morphine-ketamine combination is supported by current evidence demonstrating ketamine's opioid-sparing properties. Notably, the reduction in 24-hour morphine consumption (58% in MKG) corroborates meta-analyses that found perioperative ketamine reduces postoperative opioid use by 30–50% [14] or by 5-20mg in the first 72 hours across surgical populations [7]. This effect is particularly pronounced in abdominal surgeries, where ketamine reduces hyperalgesia and supplemental analgesic needs [15,16].

Furthermore, the MKG group demonstrated superior and sustained analgesia (significantly lower VAS scores from the postoperative 4th onward). The sustained analgesia may be attributed to ketamine-morphine's synergistic interaction, as both drugs target distinct complementary pathways. Morphine modulates acute nociception through μ-opioid receptors [17,18], while ketamine targets the neuropathic and inflammatory components of pain via NMDA receptor blockade preventing central sensitization [19,16,20]. This dual action attenuates the "wind-up" phenomenon, which motivates chronic pain development and opioid tolerance [15,16]. This is particularly effective for hepatic resection pain, which involves significant tissue trauma, diaphragmatic irritation, and inflammatory responses that promote spinal sensitization [10]. The epidural route enhances this synergy by delivering both agents directly to spinal receptors, maximizing analgesia while minimizing systemic effects [5].

Although most studies support ketamine-opioid adjunctive role, some report conflicting results. A randomized trial using pre-incisional epidural 1 mg/kg ketamine with morphine in abdominal surgery found no long-term opioid-sparing effect despite reduced intraoperative needs [20]. This discrepancy in outcomes may arise from variations in study design, ketamine dosing or timing of administration, patient populations, or the specific surgical type.

While hemodynamic parameters remained comparable between groups at most time-points, the MKG group exhibited significantly lower HR (6-24h postoperatively) and MAP (60-150 min intraoperatively), though all values remained within normal physiological ranges. This improved hemodynamic stability likely results from: 1) enhanced analgesia reducing surgical stress responses, and 2) the low-30mg epidural ketamine dose providing effective spinal NMDA receptor blockade while minimizing systemic catecholamine release due to reduced drug systemic absorption [21,22,23]. These findings demonstrate the

combination's favorable cardiovascular profile during hepatic resection.

The absence of significant adverse effects, particularly psychomimetic reactions or respiratory depression, reinforces the safety profile of this epidural regimen. This aligns with evidence showing subanesthetic ketamine doses rarely cause psychomimetic effects when administered epidurally, likely due to reduced systemic absorption compared to IV routes [7,24,16,5]. The preserved respiratory function is especially important for hepatic patients due to altered drug metabolism [5], addressing a key clinical concern about combining morphine with ketamine.

**Clinical Implications**

The epidural morphine-ketamine combination offers distinct advantages for hepatic resection patients, who face unique challenges including coagulopathy risks and altered drug metabolism. Our study focused on Child-Pugh A patients to ensure metabolic capacity while demonstrating significant pain reduction. Our approach aligns with ERAS protocols by minimizing opioid-related complications (respiratory depression, PONV) while maintaining effective analgesia. The combination's ability to reduce systemic opioid exposure without compromising pain control makes it particularly valuable for this high-risk surgical population, where optimal pain management must balance efficacy with safety concerns. Future studies should explore continuous catheter-based techniques with coagulation monitoring and include high-risk populations (Child-Pugh B/C).

**Study Limitations**

Despite benefits, our study has limitations. First, its small sample size may restrict the generalizability of results and the statistical power to identify rare adverse events. Larger trials are needed to confirm safety. Second, the single-center design may introduce selection bias. Third, we did not assess long-term outcomes, such as chronic post-surgical pain, which could provide further insights into ketamine's preventive effects. Finally, the fixed ketamine dose (30 mg) may not be optimal for all patients; individualized dosing based on pharmacokinetics may improve outcomes.

**Conclusion**

In conclusion, the addition of low-dose epidural ketamine to morphine and bupivacaine significantly enhances postoperative analgesia, delays the need for rescue opioids, and reduces total morphine consumption without increasing adverse effects in patients undergoing hepatic resection.

**Conflict of Interests**: no conflicts of interest.

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