Effects of Preincisional Analgesia with Surgical Site Infiltration with 0.25% Bupivacaine or with Ketamine in Patients Undergoing Open Cholecystectomy and Pyelolithotomy Surgery Under General Anaesthesia

Sweety Bhola¹, Ranjeeta Aske²

ABSTRACT

Introduction: Postoperative pain management remains very important in patient’s management to ensure a better quality of life. Unfortunately, adequate postoperative analgesia is achieved in a very less number of patients. Delayed postoperative mobilization because of pain reduces quality of life and delays return to normal daily activities. Preemptive analgesia is reported to inhibit the persistence of postoperative pain after surgery. The aim of this study was to assess the analgesic effectiveness of preincisional infiltration of ketamine following elective open cholecystectomy and pylolithotomy surgery as compared to 0.25% bupivacaine.

Material and methods: In this study, 60 patients, age (16 – 50yrs) ASA grade I and II are posted for open cholecystectomy and pylolithotomy surgery, randomly assigned with informed consent, into 2 groups (n=30), as; Group K: Received subcutaneous infiltration of 10 ml containing ketamine 2 mg/kg. Group B: Received subcutaneous infiltration of 10 ml 0.25% of bupivacaine. Skin infiltration was given along the incision 5 min before incision. Postoperative pain was assessed using visual analogue scale (VAS) at rest and with evaluation of additional opioid analgesic requirements.

Results: Results will be analysed by using the independent-sample Student’s t-test or Mann–Whitney test for numerical variables and P<0.005 will be considered significant. We can conclude that ketamine appears to be a promising preemptive analgesic through surgical site infiltration. VAS score in ketamine group was significantly lower than that in the bupivacaine group 8, 10, and 24 h postoperatively.

Conclusion: Ketamine group showed delayed request of additional opioid analgesia (P < 0.001) with significantly less opioid consumption (P < 0.001) as compared to bupivacaine. Ketamine has comparable effect to bupivacaine with longer duration of action and minimal adverse effects.

Keywords: Open Cholecystectomy and Pyelolithotomy Surgery, Postoperative Pain, Bupivacaine, Ketamine

INTRODUCTION

Postoperative pain management remains very important in patient’s management to ensure a better quality of life.¹ Unfortunately, adequate postoperative analgesia is achieved in less number of patients. Adverse physiological alterations due to insufficient postoperative analgesia may eventually lead to increased morbidity and mortality after surgery.² Delayed postoperative mobilization caused by pain reduces quality of life and delays return to normal daily activities in many patients after surgery.³,⁴ Preemptive analgesia is reported to inhibit the persistence of postoperative pain after surgery.

Preemptive analgesia (treating pain before its onset): The concept of providing analgesia to the patient before surgical incision, resulting in less postoperative pain.³

Application of analgesic agents in the area of the surgical incision

Reduces the number of signals generated by pain receptors (nociceptors) preventing central hypersensitivity of the CNS

reduces the incidence of pain sensation in the perioperative period

Inhibit the persistence of postoperative pain

Postoperative pain varies according to many variables which may be age, sensitivity to pain, type and duration of surgery, and type of analgesia used, judge the severity of pain and its management, other complications, etc. The aim of this study was to assess the analgesic effectiveness of preincisional infiltration of ketamine following elective open cholecystectomy and pylolithotomy surgery as compared to 0.25% bupivacaine.

MATERIAL AND METHODS

In this study, 60 patients, age (16 – 50yrs) ASA grade I and II are posted for open cholecystectomy and pylolithotomy surgery, randomly assigned with informed consent, into 2 groups; (n=30), as;

¹Senior Resident, Department of Anaesthesiology GMC and Hamidia Hospital, Bhopal, ²Associate Professor, Department of Anaesthesiology GMC and Hamidia Hospital, Bhopal, India

Corresponding author: Sweety Bhola, Senior Resident, Department of Anaesthesiology GMC and Hamidia Hospital, Bhopal, India

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Group K: received subcutaneous infiltration of 10 ml containing ketamine 2 mg/kg.
Group B: received subcutaneous infiltration of 10 ml 0.25% of bupivacaine,

The prospective, randomized study was conducted in the department of anaesthesiology at Hamidia Hospital, Bhopal, over a period of 6 months. With the help of a computer-generated table of random numbers, patients were randomized into 2 groups; all patients had an equal probability of assignment to the groups.

**Inclusion criteria:**
1) Patients age (16 – 50yrs),
2) ASA grade I and II patients,
3) All patients going for elective open cholecystectomy and pyelolithotomy surgeries.

**Exclusion criteria:**
1) ASA grade III, IV, and V or (E),
2) Patients with allergy to study drugs,
3) Cardiovascular disease (hypertension, tachycardia, congestive heart failure, and coronary artery disease), decompensated liver, renal failure,
4) History of treatment of chronic pain condition.

**All patients underwent a standardized anaesthesia protocol which included:**
- IV 0.04 mg/kg midazolam and glycopyrrolate 0.01mg/kg.
- Induction with propofol (2 mg/kg) and fentanyl (2 μg/kg).
- Succinylcholine (1mg/kg) was given and tracheal intubation performed.
- Atracurium was used as a muscle relaxant.
- Maintenance: 66% nitrous oxide and 33% O2 mixture along with isoflurane (1-2%).
- The study drugs were infiltrated subcutaneously into the incisional site region after induction of anaesthesia and surgical incisions was given only after 15 mins from the study drug administration.
- I/V fentanyl infusion 0.5μg/kg/hr in 50 ml NS was given.
- At the end of surgery, IV glycopyrrolate 0.01mg/kg and neostigmine 0.05mg/kg. Under direct vision oropharyngeal suction was done and all patient's were carefully extubated when they were able to obey commands and lung ventilation was deemed adequate.

**Monitoring:**
- ECG, Pulse rate, BP (SBP, DBP, MEAN arterial pressure), Respiratory Rate, Et-CO₂, SpO₂ were recorded intraoperatively at 0, 5, 10, 20 mins and after that every 20 mins till the end of surgery. All the parameters were compared with baseline (pre-operative) value. Recovery room complications such as nausea/vomiting, dizziness, hallucination and any allergic reaction and other side effects, if any, were also noted.

**STATISTICAL ANALYSIS**
SPSS 16 for windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Numerical variables were presented as mean and SD. The intergroup differences were compared using the independent-sample Student's t-test or Mann–Whitney test for numerical variables, Chi-square test (Fisher’s exact test) for qualitative variables. P < 0.05 was considered statistically significant.

**RESULT**
No patients were excluded from the study after enrollment. The two groups were comparable regarding age, weight, ASA class, and duration of anaesthesia and surgery [Table 1]. There were no clinically significant changes in blood pressure and HR throughout the 24 postoperative hours in the two groups [graph 1,2]. Table 2 shows that the VAS score at rest decreased significantly in Group B starting from 10 h postoperatively up to 24 h and in Group K, from 8 to 24 h as compared to the immediate postoperative reading. VAS score in ketamine group was significantly lower than that in the bupivacaine group 8, 10, and 24 h postoperatively.

Ketamine group showed delayed request of additional opioid analgesia (P < 0.001) with significantly less opioid consumption (P < 0.001) as compared to bupivacaine. The total dose of tramadol consumed during the 24 postoperative hours was significantly smaller in ketamine group (P < 0.001).

Table 4 shows sedation score was maximally up to 5 in the ketamine group and up to 3 in the bupivacaine group. There was significant difference in the VAS score and sedation score between the two groups at all time points.

**Table-1:** Baseline patient’s characteristics of the two studied groups

| Variables            | Group K (n=30) | Group B (n=30) | P value |
|----------------------|---------------|---------------|---------|
| Age (years)          | 33.8 ± 7.87   | 34.9 ± 5.97   | 0.27    |
| Weight (kg)          | 57.10 ± 8.99  | 55.23 ± 7.90  | 0.19    |
| ASA Class I/II       | 1.4 ± 0.56    | 1.3 ± 0.47    | 0.24    |
| Duration of surgery (min) | 109.17 ± 10.00 | 107.33 ± 9.44 | 0.234   |
| Anaesthetic time (min) | 125.17 ± 9.19  | 123.4 ± 8.36  | 0.219   |

Data are expressed as mean and SD. SD: Standard deviation, ASA: American Society of Anesthesiologists.
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**Graph-1:** Intraoperative hemodynamic changes (a. systolic blood pressure, b. diastolic blood pressure, c. pulse rate)

| VAS Score | Group K (n=30) | Group B (n=30) | P value |
|-----------|----------------|----------------|---------|
| At the End of surgery | 0 | 0 | NA |
| After 1st hr | 0 | 0 | NA |
| After 2nd hr | 0.37±0.49 | 0.47±0.63 | .247 |
| After 4th hr | 1.27±0.58 | 1.63±0.76 | .020 |
| After 6th hr | 2±0.52 | 2.67±0.84 | .0002 |
| After 8th hr | 2.53±0.50 | 3.7±0.83 | <.0001 |
| After 10th hr | 2 ± 0.52 | 4.67±0.84 | <.0001 |
| After 12 hrs | 3.73±0.58 | 5.5±0.82 | <.0001 |
| After 18 hrs | 4.77±0.57 | 6.47±0.75 | <.0001 |
| After 24 hrs | 5.63±0.67 | 7.47±0.68 | <.0001 |

**Graph-2:** Visual analogue score postoperatively in the two studied groups

| Sedation score | Group K (n=30) | Group B (n=30) | P value |
|----------------|----------------|----------------|---------|
| At the End of surgery | 3.87±0.51 | 2.37±0.49 | <.00001 |
| After 1st hr | 3.1±0.30 | 1.53±0.57 | <.00001 |
| After 2nd hr | 3.03±0.18 | 1.07±0.25 | <.00001 |
| After 4th hr | 3±0 | 1.03±0.18 | <.00001 |
| After 6th hr | 2.9±0.30 | 1.0 | <.00001 |
| After 8th hr | 2±0 | 0.17±0.38 | <.00001 |
| After 10th hr | 1.07±0.25 | 0.07±0.25 | <.00001 |
| After 12 hrs | 3.37±0.49 | 0 | 0.00006 |
| After 18 hrs | 0.03±0.18 | 0 | 0.164 |
| After 24 hrs | 0 | 0 | NA |

**Graph-3:** Sedation score postoperatively in the two studied groups

**DISCUSSION**

The results of this study indicate that preincisional surgical site infiltration using both ketamine and bupivacaine can provide adequate postoperative pain relief up to 24 h postoperatively following open cholecystectomy and pyelolithotomy surgery under general anaesthesia. Both drugs were safe with minimal sedation and limited adverse events. Ketamine appeared to have a longer analgesic duration compared to bupivacaine. It delayed requesting and decreased consumption of additional analgesia.

**Ketamine**

Noncompetitive antagonist of NMDA receptor that can reverse central sensitization and reduce wind-up and consequently decreases postoperative pain, which plays an important role in pain modulation. Ketamine has a local anaesthetic effect mediated by a depression of sodium-channel function. The two groups up to 8 h postoperatively, which is significantly more with group K. Afterward, sedation score was zero in all patients. Postoperative adverse effects of bupivacaine were limited to only one case of nausea. Ketamine-related adverse effects were two cases of nausea, one case of vomiting and one case of dizziness.
analgesic effect of ketamine may be increased due to its anti-inflammatory effect. It interacts with inflammatory cells recruitment, cytokines production, and inflammatory mediator regulation. Stubhaug et al.\textsuperscript{3,5} showed that ketamine decreases acute postop pain by inhibiting C-fiber activity. Preincisional infiltration of ketamine prolongs the time to first analgesic requirement and also decreases the total amount of analgesics used postoperatively.

In the current study, we tested the hypothesis that ketamine, having multiple mechanisms of action, may be effective when administered by subcutaneous injection at the surgical site prior to incision.

**Bupivacaine**

In the case of local anaesthetic agents such as bupivacaine or ropivacaine, pain evaluation is particularly important during the period of drug action (ie, the first 12 hours after their administration). Decreasing number of stimuli reaching the CNS from the nociceptors achieved through administration of local anaesthetic agents limits the development of peripheral and central sensitization. However, earlier studies found less or no beneficial postoperative analgesic effects of preemptive ketamine administered intravenously in small doses in adults undergoing abdominal hysterectomy,\textsuperscript{6} total mastectomy,\textsuperscript{7} cruciate ligament repair and other surgeries.\textsuperscript{9,10,11,12} Several previous studies demonstrated postoperative analgesic efficacy of local anesthetic infiltration of surgical site including laparoscopic gynecology, orthopedic surgery, and hernia repair.\textsuperscript{13,14}

In the present study we have shown that patients preemptively receiving bupivacaine along the line of the planned surgical incisions reported less pain intensity according to VAS.

**CONCLUSION**

We can conclude that ketamine appears to be a promising preemptive analgesic through surgical site infiltration. Ketamine has comparable effect to bupivacaine with longer duration of action and minimal adverse effects.

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