Efficacy of Low-dose Ketamine as Sole Analgesic Agent in Maintaining Analgesia and Intraoperative Hemodynamics During Laparoscopic Gynecological Surgeries

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Abstract

Background: Ketamine, in low doses, is known to possess intense analgesic properties. The available literature shows wide variation regarding the time and dose of administration of ketamine during surgery. Aim: The aim of this study was to evaluate the effect of intraoperative administration of ketamine when used as sole analgesic in low doses, on hemodynamics and postoperative analgesia in patients undergoing laparoscopic gynecological surgery and compared on the basis of duration of surgery. Settings and Design: This prospective, observational study was conducted from July to December 2015, over a period of 6 months in a tertiary care medical college and hospital. Materials and Methods: Seventy patients between 23 and 55 years planned for laparoscopic gynecological surgery were recruited. Ketamine was given in a dose of 0.5 mg/kg preoperatively and then repeated every ½ hourly in a dose of 0.25 mg/kg throughout the surgery. Hemodynamic parameters, time to the first rescue analgesia and complications were recorded for the first 8 h. Statistical evaluation was done and result expressed as percentage. Paired t-test was employed for the comparison of numerical variables within the group. Results: Seventy percent of the patients did not require any postoperative rescue analgesia during the first 8 h after surgery. None of the patients complained of pain immediately after extubation, and 16% of the patients had minor postoperative complications. The intraoperative hemodynamic profile was significantly altered. Duration of surgery and dose of ketamine required did not affect the duration of analgesia. Conclusion: Ketamine in low dose proved to be an efficacious analgesic even in the long duration laparoscopic gynecological surgeries. It stabilizes intraoperative hemodynamics thereby reducing the requirement of other anesthetic and antihypertensive agents.

Keywords: Hemodynamics, laparoscopic gynecological surgery, low dose ketamine, postoperative analgesia

INTRODUCTION

Ketamine is a popular anesthetic drug producing dissociative anesthesia. It has intense analgesic properties which outlasts its duration of anesthesia and is present even in subanesthetic doses.[1] The term “low dose” is used when ketamine is administered as bolus dose of <2 mg/kg intramuscularly and <1 mg/kg via intravenous (IV) or epidural route.[2] Laparoscopic gynecological surgery is known to cause less tissue trauma and is performed on day care basis, especially while investigating infertility. With the rapid growth and wider applicability even complex surgeries such as myomectomy, hysterectomy is being routinely performed laparoscopically. These surgeries, however, entail more tissue handling, longer duration of surgery, and concomitant increase in pain. For adequate prevention of pain, ketamine needs to be used throughout the surgery to reduce the sensitization of central and peripheral pain pathways. The adequacy of the ketamine administration schedule, therefore, is an important aspect for pain prevention.[3] The studies done previously have used single preemptive dose of ketamine with conflicting results.[4-14] Besides in all these studies, additional analgesic adjuncts have been used. Regular intraoperative dosing in the form of repeated boluses or continuous infusion has been studied previously in open surgery. This study is unique in the...
sense that it tests both preemptive and intra-operative effect of ketamine in a dose of 0.5 mg/kg/h without any other analgesic adjunct, in patients undergoing laparoscopic surgery. We have also evaluated the effect of duration of surgery on analgesic efficacy of ketamine.

Materials and Methods

This prospective, observational study was conducted from July to December 2015 over a period of 6 months. After getting clearance from the Institutional Ethical Committee, 70 females who were planned for laparoscopic gynecological surgery were recruited for the study and a written informed consent was obtained. The age range of the patients was 23 years to 55 years, and all patients belonged to the American Society of Anesthesiologists (ASA) Class I and II.

Patients who had history of allergy to opioids or ketamine, drug abuse, psychiatric illness or communication difficulties, chronic pain syndrome, and alcohol abuse were excluded from the study. Similarly, patients receiving regular opioids or drugs with known analgesic properties within 24 h before the surgery were also excluded from the study. Patients belonging to ASA class III, IV, or V were not included in the study.

Before shifting the patients for surgery, visual analog scale (VAS) scale was explained to all the patients. The drugs were administered by anesthesiologist. No other analgesic drug was planned to be added other then fentanyl in the study. Hence, no control group was included due to ethical issues. As single drug was to be given, no drug coding was done. All the patients were given glycopyrrolate 0.2 mg and midazolam 1 mg both by IV route. This was followed by IV ketamine 0.5 mg/kg (Ketlar® themis). Induction was done with IV administration of propofol 1.5–2 mg/kg, fentanyl 2 μg/kg, and succinylcholine 1.5 mg/kg. After oral endotracheal intubation, anesthesia was maintained with sevoflurane 1.6%–2% and 60% O₂ in O₂, and muscle relaxant used was atracurium. Ketamine was repeated every ½ hourly in a dose of 0.25 mg/kg till the end of surgery. Exubation was done after adequate reversal with IV neostigmine 2.5 mg and glycopyrrolate 0.5 mg. No analgesic was given other than the initial dose of fentanyl. Wound infiltration was also not done at the time of closure.

Hemodynamic parameters such as pulse rate and blood pressure (BP) were recorded by the anesthesiologist conducting the case. Recordings were made preoperatively, just after intubation and every 30 min thereafter till extubation. Nitroglycerin, clonidine, and esmolol were used to counteract the effects of carboperitoneum. Postoperatively, pain was assessed by VAS score up to 8 h. The assessment was done by the same anesthetist in all the cases. Rescue analgesia in the form of injection diclofenac 75 mg IV was given when VAS score equaled or exceeded the value of 4 and time to the first rescue analgesia was noted. Injection tramadol 100 mg was given in those patients where nonsteroidal anti-inflammatory drugs (NSAID) was contraindicated. Any significant intraoperative findings, duration of surgery, total amount of ketamine used, and immediate postoperative complications were recorded additionally.

Results

The mean age in the study was 35.29 ± 9.89 years. Various gynecologic laparoscopic surgeries were performed in the selected 70 patients [Table 1]. Thirteen patients had associated comorbidities such as hypothyroidism, diabetes, and hypertension. Duration of anesthesia was calculated from the time of induction of anesthesia to extubation, and it ranged from 20 min to 3 h with a mean of 77.14 min. Patients were divided into six groups based on the duration of anesthesia. Various parameters such as dose of ketamine required, patients requiring no rescue analgesia (expressed as percentage), body mass index, and postoperative complications (expressed as percentage) were contrasted with the duration of surgery [Table 2].

None of the patients complained of pain immediately after extubation and were comfortable when shifted to recovery. In 49 patients (70%), no postoperative rescue analgesia was required even 8 h after surgery irrespective of the duration of surgery. In only 10 patients (14%), rescue analgesia with diclofenac was required within 1 h after extubation.

Hemodynamic parameters such as systolic BP (SBP), diastolic BP (DBP), and pulse rate were recorded preoperatively, after induction and every ½ hourly subsequently till extubation. Paired Student’s t-test was used to evaluate the effect of ketamine on these hemodynamic parameters [Table 3]. P < 0.05 was considered statistically significant for 95% confidence interval. SBP was decreased significantly at the time of induction. Intraoperatively, there was a significant reduction in SBP and pulse rate from the preoperative value, but the variations in DBP were not significant statistically. At the time of extubation, all three parameters, i.e., SBP, DBP, and pulse rate increased tremendously, and these variations were statistically significant [Table 3]. The variations in SBP, DBP, and pulse rate have been depicted in Graphs 1-3.

Postoperative complications were observed in only 11 patients [Table 4]. All these patients had minor postoperative complications which were treated medically with good

| Table 1: Various laparoscopic gynecological procedures performed |
|---------------------------------------------------------------|
| Name of surgery                                            | Number of patients |
| DHL                                                          | 26               |
| TLH                                                          | 35               |
| Laparoscopic myomectomy                                      | 5                |
| Laparoscopic salpingo-oophorectomy                           | 2                |
| Laparoscopic ovarian cystectomy                              | 2                |
| DHL=Diagnostic hysteroscopy and laparoscopy, TLH=Total laparoscopic hysterectomy |

Compliance with ethical standards: The authors declare that they have no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients gave the informed consent as per institutional regulations.
recovery. Delayed awakening was not noticed in any of our
patients despite the long duration of surgery. In only three
patients (4%), the Ramsay sedation score of five was observed
just after extubation.

**DISCUSSION**

This study was conducted to evaluate the efficacy of ketamine in
a dose of 0.5 mg/kg as analgesic agent not just preemptively but
repeated hourly in the intraoperative period as well. Single dose
of fentanyl (2 μg/kg) was given only at the time of induction,
and no other analgesic was used. The aim of this study was to
test the analgesic efficacy and not its opioid sparing effects. Our
results demonstrate that ketamine when given preemptively as
well as intraoperatively not only provides long-lasting
analgesia but also improves intraoperative hemodynamics
even in long duration laparoscopic gynecological surgeries.
This is the only study which not only proves the analgesic
efficacy of ketamine but also highlights the effect of duration
of surgery on ketamine.

The number of patients requiring rescue analgesia in the first
8 h postoperatively did not increase linearly with the increase
in duration of the procedure. Almost 93% of the patients did
not require analgesia till 8 h when the duration of surgery was
about 30 min. This can be attributed to minimal tissue handling
and continuance of effect of fentanyl in short procedures. It
is important to note that in our study, the majority of patients
did not require rescue analgesia despite undergoing prolonged
procedures of up to 3 h. This emphasizes the need for repeated
administration of low-dose ketamine intraoperatively for
better postoperative analgesia. The prolongation of surgical
procedure in this study was either due to dense intraabdominal
adhesions or due to morcellation of viscera in our study. The
maximum analgesic requirement was seen in patients in whom
surgery lasted for 30–90 min. Ketamine given intraoperatively
resulted in better pain control in patients having dense
intraabdominal adhesions. Five out of seven patients having
dense abdominal adhesions did not require rescue analgesia
till 8 h postoperatively. A systematic review by Laskowski
et al., included published studies from 1966 to 2010 using
IV ketamine (bolus or infusion) to decrease postoperative
pain. The studies using any form of regional anesthesia were

| Duration (min) | Number of patients | Mean age±SD (years) | BMI | Mean ketamine required (mg/kg) | Number of patients (%) requiring no rescue analgesia till 8 h | Postoperative complications |
|---------------|--------------------|---------------------|-----|-------------------------------|-------------------------------------------------------------|----------------------------|
| <30           | 14                 | 29.79±5.6           | 22.84 | 0.51                          | 13 (93)                                                     | 2                          |
| 31-60         | 20                 | 28.55±4.7           | 24.03 | 0.71                          | 14 (70)                                                     | 4                          |
| 61-90         | 14                 | 36.29±10.7          | 21.59 | 0.97                          | 8 (57)                                                      | 2                          |
| 91-120        | 9                  | 41.22±6.2           | 25.43 | 1.19                          | 6 (67)                                                      | 1                          |
| 121-150       | 8                  | 46.5±11.2           | 25.71 | 1.34                          | 5 (62)                                                      | 2                          |
| 151-180       | 5                  | 46.2±2.4            | 22.06 | 1.66                          | 3 (60)                                                      | 0                          |

BMI=Body mass index, SD=Standard deviation
Table 3: Changes in various hemodynamic parameters before, during and after surgery

| Duration (min) | SBP (mean) | $P$ | DBP (mean) | $P$ | Pulse (mean) | $P$ |
|---------------|------------|-----|------------|-----|--------------|-----|
| Preoperative  | 127.7      |     | 78         |     | 92.87        |     |
| Postinduction | 124.97     | 0.23| 82.21      | 0.04*| 106.82       | <0.0001*|
| 30            | 119.98     | 0.002*| 81.89      | 0.07| 88.70        | 0.36 |
| 60            | 119.61     | 0.0002*| 79.14      | 0.75| 82.3         | 0.04*|
| 90            | 118.90     | <0.0001*| 80.19      | 0.67| 78.24        | 0.0004*|
| 120           | 119.35     | 0.0005*| 78.88      | 0.4 | 75.85        | 0.004*|
| 150           | 112.8      | 0.01* | 75.4       | 0.1 | 79.4         | 0.23 |
| Postextubation| 135.25     | 0.0007*| 88.29      | <0.0001*| 106.77    | <0.0001*|

*Significant ($P<0.05$). SBP=Systolic blood pressure, DBP=Diastolic blood pressure.

dosing regimens were used. Unlike our study where ketamine is the sole analgesic agent, additional analgesic agents such as paracetamol, tramadol, ketoprofen, and/or epidural analgesia were used in these studies; hence, analgesic effect can obtained cannot be attributed to ketamine only. Argiriadou et al. studied preincisional and repeated intraoperative use of ketamine in patients undergoing major abdominal surgery with epidural and general anesthesia. They reported smaller pain scores than those who received placebo after awakening and 3 and 6 h later. Mendes et al. in their study found that perioperative use of $S(+)$-ketamine is better than intraoperative use in patients undergoing major abdominal surgery. This finding disagrees with our observation probably due to the type of surgery. Major abdominal surgery produces more tissue trauma as compared to laparoscopic gynecological surgery.

Intraoperative hemodynamic parameters were better controlled with the use of ketamine. Ketamine affects reflex sympathetic response due to laryngoscopy by preventing rise in SBP, but DBP and pulse showed significant increase at the time of intubation [Table 3]. The reduction was within the 20% range of baseline indicating a good hemodynamic stability even in the presence of capnoperitoneum. The requirement of propofol and other antihypertensive drugs was also observed to be reduced intraoperatively. Postoperative complications were few and easily managed by medications. Psychomimetic reactions were observed in the three patients who responded well to midazolam. It is important to note that the rate of complication depends neither on the dose of ketamine nor on the duration of surgery. The rate of complications in our study is comparable with other such previous studies.

Opoids have been used as the primary analgesic agent for management of acute postoperative pain after any major surgery; however, opioid-related adverse effects inhibit rapid recovery and rehabilitation. The repeated use of ketamine in a dose of 0.5 mg/kg/h for analgesia has allowed us to counter such adverse effects.

The main limitation of our study was the short duration of follow-up. Long-term follow-up regarding mechanical hyperalgesia and the residual pain was not done. In this study, nitrous oxide was used which is known to enhance the analgesic efficacy of subanesthetic doses of ketamine as reported by Corssen and Domino. It may have enhanced
N-methyl-D-aspartate (NMDA) receptor inhibition by ketamine as it has been reported to exert NMDA antagonist properties. Its effect, however, extending to postoperative period is controversial. No control group was included in this study as use of other analgesics such as NSAIDs or opioids would have interfered with the assessment of analgesic efficacy of ketamine. Using no analgesic in the control group would have been ethically not permissible.

It remains to be seen whether the results of this study can be replicated when oxygen air mixture is used and in surgeries where tissue trauma and hence pain component is more. Further studies can be planned, in which efficacy of ketamine in the above-mentioned dose is compared with NSAIDs or opioids.

**Conclusion**

Ketamine in a dose of 0.5 mg/kg/h provides good postoperative analgesia with minimal side effects and can be used as sole analgesic agent in laparoscopic gynecological surgeries. Ketamine in low dose shows good hemodynamic control and significantly decreases the need of rescue analgesia even in the long duration surgeries and in patients where NSAIDs are contraindicated.

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**Conflicts of interest**

There are no conflicts of interest.

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