

Ketamine for preemptive analgesia in major gynaecologic surgery

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Abstract

Background: It has been suggested that the prolonged pain and hyperalgesia occurring after an injury is due to central sensitization in the spinal cord. N- methyl D- Aspartate (NMDA) receptors are activated by glutamate and aspartate and have been implicated in the wind-up phenomenon of central sensitization. Ketamine blocks the NMDA receptor sites and has been suggested to provide preemptive analgesia. This study was designed to assess the pre-emptive analgesic effect of ketamine in Nigerians.

Method: Two groups of twenty patients scheduled for intra-abdominal gynecological operation were randomly assigned to receive either 0.5mg/kg ketamine pre-incision or post incision. They all had standard general anaesthesia with pentazocine for intra-operative analgesia. Post-operatively, the time to first request for analgesia (TFA) and pain intensity, using the visual analogue scale (VAS) at that time were noted. Pain intensity was also scored at 4, 8, 12 and 24 hours. Adverse reactions and patient satisfaction were recorded.

Results: The TFA for the pre-incision group was significantly longer than the post-incision group. The pain intensity scores at the periods measured were not significantly different in both groups.

Conclusion: It is concluded that at 0.5mg/kg body weight, ketamine prolongs the TFA but a sustained preemptive effect of ketamine could not be demonstrated.

Key words: Preemptive analgesia, ketamine

Introduction

Ketamine is an anaesthetic agent with profound analgesic actions. The site of its analgesic effects have been suggested to be noncompetitive at the NMDA and non-NMDA glutamate receptors and opioid receptors in the central nervous system.¹⁻³

When noxious stimuli from surgical injury reach the central nervous system a state of sensitization occurs which has been termed the wind up phenomenon.⁴ The primary excitatory neurotransmitters, glutamate and aspartate, which mediate pain are released in the spinal cord and their NMDA receptor sites are activated

leading to a state of hyperalgesia.⁴

The concept of preemptive analgesia was developed when results of animal experiments showed that the administration of an analgesic before noxious stimulation attenuated that hyperalgesia with improved pain relief.⁵ The human studies employing local anaesthetic agents and opioids however yielded equivocal results prompting further research into this phenomenon.⁶ Since Ketamine is a direct blocker at the receptors involved in central sensitization, studies have explored the preemptive effect of ketamine but mixed results have also been reported. While a preemptive effect was observed after intravenous administration with low doses by Roytblat et al 1993⁷ and Suzuki et al 1999,⁸ and after epidural administration,^{9,10} other workers¹¹ have failed to demonstrate a preemptive effect.

In Nigeria and some other developing nations, ketamine is a commonly employed anaesthetic because it is cheap and perceived to be safe, compared to the developed countries where it is used reservedly in view of its hallucinatory side effects. However despite this widespread use there is paucity of reports of either a preemptive or prolonged postoperative analgesic effect. The aim of this study is to find out if there is a preemptive effect of ketamine.

Patient and methods

This is a double-blind randomized placebo controlled study of forty American Society of Anesthesiology (ASA) physical status classifications I and II adults scheduled for major abdominal gynaecologic surgery. The exclusion criteria were a history of cardiovascular diseases, central nervous system and psychiatric disorders and chronic analgesic use. Informed consent was obtained and they were randomized into two groups of twenty to receive 0.5mg/kg

body weight ketamine hydrochloride pre surgical incision or post surgical incision. They were instructed on the use of the visual analogue scale for pain intensity the day before the operation and had psychological preparation, analgesic premedication being omitted.

For both groups, anaesthesia was induced with thiopentone sodium 5mg/kg body wt. with endotracheal intubation and muscle relaxation facilitated with pancuronium bromide 0.1mg/kg body wt. Anaesthesia was maintained with 50% nitrous oxide in oxygen and 0.5 -1% Halothane. Intraoperative analgesia was with 0.5mg/kg body wt of pentazocine, which was given after the study agents had been administered. The anaesthetist was blinded to the study medications, which were made up in 5ml syringes labeled A and B, with either syringe containing ketamine or the placebo normal saline. A was administered 10 minutes pre incision and B was administered about 10-20 minutes post incision. Other necessary intra-operative care was left to the discretion of the anaesthetist. At the end of the procedure, the residual effects of pancuronium were reversed with neostigmine and atropine and the patient was transferred to the recovery ward.

Postoperatively, the time to first request for analgesic was noted and the Visual Analogue Score (VAS) of pain intensity at that time was noted. Postoperative analgesia was with intramuscular pentazocine 45 – 60mg 4 hourly. Visual Analogue Scores were recorded at 4, 8, 12 and 24 hour postoperatively. Hallucinations and nausea and vomiting were specifically enquired into and recorded and other complications were noted.

The patients' satisfaction with analgesia was documented. Statistical analyses were performed using the EPIINFO 6.0 statistical package. Group averages were reported as mean and standard deviations. The differences

in the pain scores were analyzed by the paired t-tests, a P value < 0.05 was considered statistically significant.

Results

The pre-incision ketamine (PIK) and the post-incision ketamine (POK) groups were comparable in age (mean age 33.4 ± 8.8 Vs 32.2 ± 12.5 years), weight (mean weight 56 ± 10.4 Vs 59 ± 6.4 kg) and duration of surgical procedure (mean 136 ± 27.5 Vs 133 ± 24 minutes). Twenty-six patients had total abdominal hysterectomy, seven had myomectomy while the rest had tubal surgery. Each

patient had 30 mg of pentazocine and this was administered soon after the study drug B was given. The TFA for the PIK group was significantly longer than the POK group 153.5 ± 89 and 109.0 ± 86.6 minutes, $P = 0.04$, but the VAS pain intensity scores at that time were comparable. In the other study periods, the pain intensity scores were lower for the PIK group but did not attain statistical significance (Table 1).

No patient suffered hallucinations. Vomiting was recorded in 5 (25%) of patients in each group. All patients but one in the PIK group expressed satisfaction with the management.

Table 1: VAS pain scores (cm) between the pre-incision (PIK) and the post-incision ketamine (POK) groups (mean \pm standard deviation)

Period	Pre-incision ketamine	Post-incision ketamine	p value
TFA (min)	153.5 ± 89	109.0 ± 86.6	0.04*
VAS at TFA	5.36 ± 1.87	6.8 ± 2.1	0.08
VAS at 4 hr	3.8 ± 2.3	5.2 ± 2.06	0.1
VAS at 8 hr	3.7 ± 2.1	3.75 ± 2.4	0.16
VAS at 12 hr	3.4 ± 1.4	4.5 ± 2.2	0.12
VAS at 24 hr	3.1 ± 1.3	3.9 ± 1.9	0.2

TFA = Time to first request for analgesic (minutes)

VAS = 10 cm Visual Analogue Scale for pain intensity

*Significant

Discussion

Our findings indicate that ketamine administered before incision prolonged the time to first request for analgesic and pain intensity at that time was lower than when the ketamine was given after incision. A preemptive effect of ketamine cannot be claimed since beyond this time a statistically significant difference between the two groups was not demonstrable. With 0.25-mg/kg i.v ketamine, Roytblat et al ⁷ found a preemptive effect. They compared

patients who had ketamine to those who did not receive ketamine at all and postoperative opioid consumption was used as an end point. Our study compares with that of Fu et al ¹², where reduction in wound pain could not be demonstrated with similar doses of ketamine but opioid-sparing effect was again demonstrated with preemptive ketamine. Owing to unavailability of equipment we were unable to further measure the analgesic consumption with a patient-controlled analgesia (PCA) machine although PCA algesimetry does not necessarily equate

pain intensity.

Taking advantage of the multiple sites of action of ketamine at the central nervous system, studies on epidural ketamine have also yielded inconclusive results with Choe et al⁹ and Aida et al¹⁰ reporting positive effects while Kucuk et al¹¹ could not detect a preemptive effect. When Abdel-Ghaffa et al¹⁵ compared pre-incision and 20-minute post-incision epidural ketamine, pain intensities were not different between the groups but opioid consumption was reduced in the pre-incision treatment group.

The failure of the present study to show a significant preemptive effect of ketamine adds to the controversy regarding the concept of preemptive analgesia. Recent evidence suggests that postoperative pain is a product of both peripheral and central sensitization.¹⁴ After free nerve endings have been stimulated by incision, cutting and traction, chemical mediators of pain such as bradykinin and prostaglandin maintain the pain longer with resultant primary hyperalgesia. The development of secondary hyperalgesia is facilitated when A alpha and A beta nerve fibres, which do not normally mediate pain, are so induced when peripheral sensitization occurs.¹⁴ Therefore to achieve sustained preemptive analgesia, pain of the initial injury must be blocked and since chemical mediators continue to be released for longer than the initial insult, their effects must be prevented for a longer time than the duration of action of a single dose of analgesic administered.

Further more, Kissin¹⁵ states that preemptive analgesia may be difficult to prove for other reasons such as that during the surgical procedure analgesics are included in the anaesthetic agents used and they themselves may exert a partial preemptive effect, a situation which we averted by the use of the same anaesthetic technique and agents in our study. Our study of postoperative pain after major gynaecologic surgery eliminated the non-

standardization of the surgical stimulus that has also been considered causal to the difficulty in proving preemptive analgesia. A current thought¹⁶ suggests that a sustained preemptive effect would therefore include neural blockade before the noxious surgical stimulus and continuation of analgesia through the intraoperative and into the postoperative period to block nociceptive input. The single dose of ketamine employed in this study, reduced pain initially and delayed the onset of central sensitization.

The absence of characteristic dreams and hallucinations of ketamine observed in this study is similar to another report¹⁷ and is probably due to the small doses and the other agents used in the anaesthetic technique.

The recent interest in ketamine is attractive in developing countries the drug is frequently used in large doses as sole anaesthetic for surgery. A prolonged analgesic effect would be expected and would have been observed in the postoperative period. Thus, comparing ketamine with thiopentone for the induction of anaesthesia for caesarean section, Kee et al¹⁷ reported TFA was longer and opioid consumption was less in the ketamine group.

In conclusion, in situations where high-tech postoperative analgesic techniques are unavailable and strong opioid analgesics are scarce the report of longer TFA of our study and less opioid requirement of other studies suggest that better initial postoperative analgesia may be achieved when ketamine (when not contraindicated) is included in the anaesthetic agents.

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