The Role of Pre-induction Ketamine in the Management of Postoperative Pain in Patients Undergoing Elective Gynaecological Surgery at the University Hospital of the West Indies

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ABSTRACT

Objectives: *To determine if a single preoperative dose of ketamine hydrochloride reduces the narcotic analgesic requirements and/or pain scores reported by patients in the first 24 hours postoperatively.*
Methods: *A single-centred, prospective, case-control study was conducted on 84 patients aged 18–65 years, American Society of Anaesthesiologists (ASA) I and II, undergoing elective gynaecological procedures at the University Hospital of the West Indies (UHWI). Patients were randomly assigned to one of two treatment groups: (a) ketamine group, where patients received intravenous ketamine 0.15 mg/kg pre-induction of anaesthesia; and (b) placebo group, patients received normal saline. The anaesthetic technique was standardized. Postoperatively, patients were interviewed at 15-minute intervals for the first hour, then at 2, 4, 6, and 24 hours to determine their pain scores and any side effects. Timing and dose of opioid analgesics were also recorded.*
Results: *The mean cumulative morphine dose over the first 24 hours postoperatively was 29.6 ± 10.8 mg for the ketamine group and 31.9 ± 11.2 mg for the placebo group (*p *= 0.324). There was also no significant difference in pain intensity measured by the visual analogue scale (VAS) between the groups. Patient age and the type of surgery performed were not found to influence pain intensity. The most common adverse effects were nausea and vomiting (32.5%), dizziness (42.2%), drowsiness and sedation (45.8%) with no significant difference between groups. Both groups had an average in-hospital stay of three days postoperatively, however, the patients in the ketamine group reported higher satisfaction scores than those in the placebo group (*p *= 0.039).*
Conclusion: *Despite no significant reduction in postoperative narcotic requirements or pain intensity, more patients who received ketamine reported higher levels of satisfaction with their pain management.*

Keywords: Ketamine, postoperative analgesia

El Papel de la Ketamina de Pre-inducción en el Tratamiento del Dolor Postoperatorio en Pacientes que se Someten a Cirugía Ginecológica Electiva en el Hospital Universitario de West Indies

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RESUMEN

Objetivos: *Determinar si una sola dosis preoperativa de hidrocloruro de ketamina reduce los requerimientos de analgésicos narcóticos y/o puntuaciones de dolor reportados por los pacientes en las primeras 24 horas posteriores a la operación.*
Métodos: *Se llevó a cabo un estudio de caso-control, prospectivo, monocéntrico en 84 pacientes de 18–65 años de edad, sometidas a procedimientos de ginecología electiva en el Hospital Universitario de West Indies (HUWI). Los pacientes fueron asignados aleatoriamente a uno de dos grupos de tratamiento: (a) grupo ketamina, en el que los pacientes recibieron una preinducción de anestesia de 0.15 mg/kg de ketamina intravenosa; y (b) grupo placebo, en el que los pacientes recibieron una*

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solución salina normal. La técnica anestésica fue estandarizada. Postoperatoriamente, se entrevistaron los pacientes a intervalos de 15 minutos durante la primera hora, y más tarde a 2, 4, 6, y 24 horas para determinar sus puntuaciones de dolor, y efectos cualesquiera. También se registraron el tiempo y la dosificación de los analgésicos.

Resultados: *La dosis promedio de morfina cumulativa promedio en las primeras 24 horas posteriores a la operación, fue de 29.6 ± 10.8 mg para el grupo de ketamina; y 31.9 ± 11.2 mg para el grupo placebo (p = 0.324). No hubo tampoco ninguna diferencia significativa entre los grupos, en cuanto la intensidad de dolor medida mediante la escala visual analógica (EVA). No se halló que la edad del paciente y el tipo de cirugía realizada tuvieran influencia en la intensidad de dolor. Los efectos adversos más comúnes fueron náusea y vómito (32.5%), vértigo (42.2%), adormecimiento y sedación (45.8%), sin diferencia significativa entre los grupos. Ambos grupos tuvieron una estancia intra-hospitalaria promedio de tres días tras la operación. No obstante, los pacientes del grupo de la ketamina reportaron puntuaciones de mayor satisfacción que los del grupo placebo (*p = *0.039).*

Conclusión: *Si bien no hubo una reducción significativa en cuanto a requerimientos de narcóticos o intensidad de dolor postoperatorios, más pacientes que recibieron ketamina reportaron niveles más altos de satisfacción con el tratamiento del dolor.*

Palabras claves: Ketamina, analgesia postoperatoria

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INTRODUCTION

Postoperative pain results from the incision and manipulation of tissues during surgery and may contribute to considerable patient suffering and prolong hospital stay (1). Pain causes an increase in the sympathetic response of the body with subsequent rise in heart rate, cardiac work and oxygen consumption. Prolonged pain can reduce physical activity and lead to venous stasis and an increased risk of deep vein thrombosis and consequent pulmonary embolism. In addition, there can be widespread effects on intestinal and urinary tract motility which may lead, in turn, to postoperative ileus, nausea, vomiting and urinary retention (2).

The goals of postoperative pain management are to reduce or eliminate pain and discomfort with a minimum of side effects and as cheaply as possible. Adequacy of postoperative pain control is one of the most important factors in determining when a patient can be safely discharged from a surgical facility and has a major influence on the patient's ability to resume their normal activities of daily living (3). Effective pain relief may also reduce the incidence of chronic pain syndromes (2). Factors affecting the degree of postoperative pain include the patient's previous experiences and mental preparation, intra-operative pain management, the nature and duration of surgery, the site and size of the incision and the extent of surgical trauma (1).

For many years, the standard method of treating postoperative pain in the developing world has been intramuscular opioids (usually morphine or pethidine). The effects of opioid drugs vary greatly among patients and thus individual responses cannot be predicted. Pain is thought to be inadequately treated in as many as one half of all surgical procedures (4). Many studies have shown that undertreatment of acute postoperative pain occurs because doctors and nurses overestimate the length of action and the strength of the drugs and that they have fears about respiratory depression, vomiting, sedation and dependency (2).

Several studies have demonstrated a decrease in opioid requirements postoperatively, as well as improved mood, following administration of sub-anaesthetic doses of ketamine perioperatively (5–13). Adverse effects were mild or absent (14). Ketamine has been used as a single intravenous dose pre-incision, as an intravenous infusion intra-operatively and up to 48 hours postoperatively, and *via* the epidural route. Its mode of action may be related to its ability to inhibit central N-methyl-D-aspartate (NMDA) receptors (15).

Modalities of postoperative analgesia, such as epidural analgesia and patient controlled analgesia (PCA) require equipment, drugs and additional staffing which are not consistently available and increase the cost of care considerably. Ketamine is readily available at the University Hospital of the West Indies (UHWI) and is relatively inexpensive. Preoperative ketamine is a potentially useful adjunct in the treatment of postoperative pain, but has not been widely studied in the local population.

SUBJECTS AND METHOD

A single-centred, prospective, patient-blinded case control study was conducted at the UHWI during the period October 1, 2009 to August 31, 2010. Approval was obtained from The University Hospital of the West Indies/University of the West Indies/Faculty of Medical Sciences Ethics Committee (ECP 275, 2008/2009), and all patients gave written informed consent. It was determined that a sample size of 42 patients per group was required to detect a 30% reduction in morphine consumption at a power of 90% and a 5% significance level (5). Inclusion criteria were patients scheduled for elective gynaecological surgery who were American Society

of Anaesthesiologists (ASA) physical status I or II, and between 18 and 65 years. Patients with any history of psychiatric disorder, chronic pain syndrome and drug or alcohol abuse were excluded. Patients receiving regular opioids or other analgesic drugs in the 24 hours before surgery were also excluded.

Patients were randomly assigned to one of two treatment groups: (a) ketamine group: patients received low dose intravenous ketamine 0.15 mg/kg (made up to 10 ml with normal saline) immediately before the induction of anaesthesia; (b) placebo group: patients received 10 ml normal saline. Study drugs were prepared and administered by the anaesthetist providing care to the patient. The patient, but not the anaesthetist (for ethical and safety reasons), was blinded to the assigned group. A standardized anaesthetic technique was used. No pre-anaesthetic medication was prescribed and the patients were fasted from the midnight before surgery. In the operating room, routine monitoring was applied. Anaesthesia was induced with propofol 2 mg/kg and morphine 0.15 mg/kg IV. Cistracurium 0.2 mg/kg was administered to facilitate tracheal intubation. Anaesthesia was maintained with nitrous oxide and isoflurane 0.5%–1.0% in oxygen. The lungs were mechanically ventilated, and the end-tidal carbon dioxide concentration maintained between 5.0% and 5.5%. The attending anaesthetist was allowed to administer further morphine boluses based on their assessment of patient needs. At the end of surgery, the volatile agent was discontinued, and residual neuromuscular blockade antagonized by neostigmine 40 µg/kg and atropine 20 µg/kg. The trachea was extubated when the patient was fully awake.

After surgery, all patients were monitored in the post-anaesthesia care unit (PACU). The nurses were blinded to prevent bias. They recorded analgesics administered as well as any side effects noted. The need for analgesia was determined by a visual analogue scale (VAS), the patient's request for analgesia and clinical parameters, such as tachycardia and hypertension. The severity of pain and sedation level were measured at 15-minute intervals for the first hour and then at 2, 4, 6 and 24 hours after surgery. The analgesic regime for the patients once transferred to the ward was written by the gynaecologists without anaesthetic input. Severity of pain was graded using a 100-mm VAS printed on a sliderule bar (Astra USA Inc, Westborough, MA). Sedation was scored as 1 = alert, 2 = asleep, alert after arousal, 3 = asleep, drowsy after arousal, 4 = asleep, difficult to rouse and 5 = unarousable. At the end of the study period, the patient gave the overall satisfaction with the pain management employed using the verbal rating scores (VRS) 0–4 (poor, fair, good, very good, excellent).

Data were collated and analysed in SPSS version 12. Chi-square tests and independent sample tests were used to determine the *p*-value. In order to compare total opioid consumption postoperatively (recovery room and ward), pethidine doses were converted to equivalent morphine doses using conversion tables (16).

RESULTS

During the study period of October 1, 2009 to August 31, 2010, a total of 300 women had gynaecological surgery at the UHWI. Eighty-four of these patients satisfied the inclusion criteria and consented to participate in the study. Forty-two patients were given ketamine (Group 1) and the remainder (42) served as the control. The mean age for patients in the ketamine group was 47.5 ± 10.1 years (range 27–65, median 45 years). The mean age for the placebo group was 44.5 ± 10.8 years (24–65, median 45 years). Total and subtotal abdominal hysterectomies were the most frequently performed procedures, accounting for 42.5%. Other procedures included myomectomies (22.6%), vaginal hysterectomy with or without anterior/posterior repair (15.5%), oophorectomy/cystectomy (10.7%) and others (6.0%) such as staging laparotomy, Wertheim's hysterectomy and cone biopsy (Fig. 1).

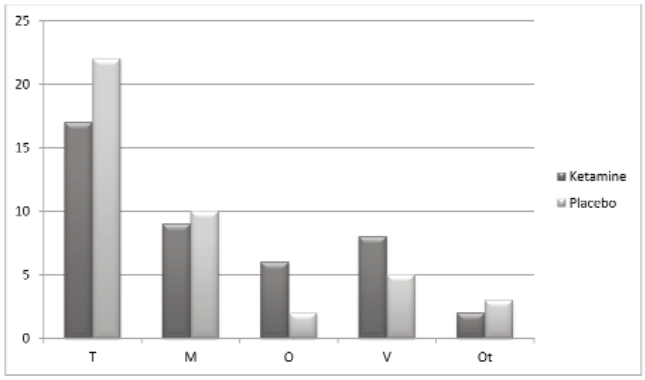

Fig. 1: The type and frequency of surgery performed on study patients.

T = Total and sub-total hysterectomy
M = Myomectomy
O = Oophorectomy/Cystectomy
V = Vaginal hysterectomy ± anterior/posterior repair
Ot = Other (Staging laparotomy, Wertheim's hysterectomy and cone biopsy)

The mean intra-operative morphine dose for the ketamine group was 13.0 ± 4.2 mg and for the placebo group was 14.3 ± 4.6 mg ($p = 0.18$). The mean morphine dose administered in the recovery period was 4.5 ± 3.7 mg and 4.5 ± 3.5 mg, in the ketamine and placebo groups, respectively ($p = 0.98$). The mean pethidine consumption on the wards post-operatively was 170.4 ± 79.5 mg and 188.1 ± 77.1 mg in the ketamine and the placebo groups, respectively ($p = 0.8$). The mean cumulative postoperative morphine dose for the keta-mine group was 29.6 ± 10.8 mg and 31.9 ± 11.2 mg for the placebo group [$p = 0.324$] (Table 1).

There was no significant difference in the time between the end of surgery and first request for analgesia between the groups. However, the ketamine group had more patients receiving analgesia greater than 150 minutes postoperatively, 69.1% *vs* 54.8% in the placebo group ($p = 0.54$). Pain intensity (VAS) was not significantly different between the groups at any of the time intervals investigated (Fig. 2).

Table 1: Comparison of analgesic consumption between ketamine and placebo groups

Analgesia and Timing	Group	Mean Dose (SD)	*p*-value
Intraoperative Morphine	Ketamine	13.0 (4.2)	0.18
	Placebo	14.3 (4.6)	
PACU Morphine	Ketamine	4.5 (3.7)	0.98
	Placebo	4.5 (3.5)	
Ward Pethidine	Ketamine	170.4 (79.5)	0.8
	Placebo	188 (77.1)	
Cumulative postoperative morphine equivalent	Ketamine	29.6 (10.8)	0.324
	Placebo	31.9 (11.2)	

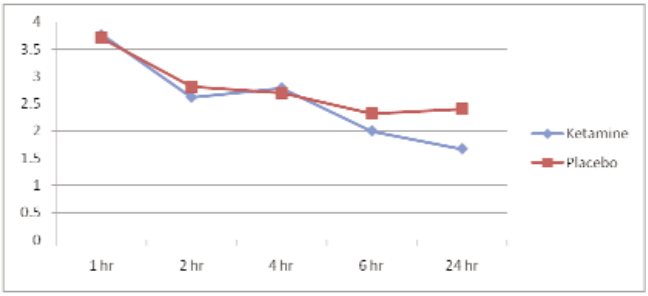

Fig. 2: The average visual analogue score (VAS) for ketamine *vs* placebo groups at each time interval assessed.

However, the ketamine group had more patients reporting no pain at 24 hours postoperatively (64.3%) *versus* 42.9% in the placebo group [$p = 0.24$] (Fig. 3). There was no association

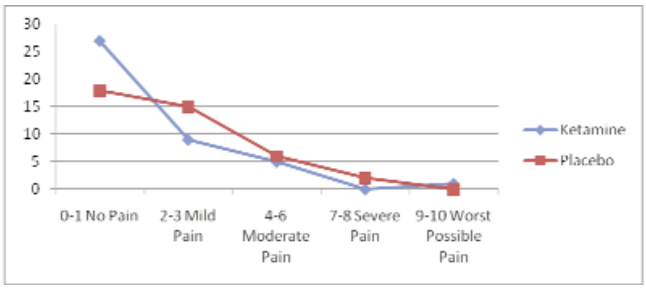

Fig. 3: The visual analogue score (VAS) recorded at 24 hours for the ketamine and placebo groups.

between the type of surgery performed or age and pain intensity between the groups. There was no difference in the level of sedation postoperatively between groups, except at two hours, when more of the patients in the ketamine group were awake in comparison to the placebo group ($p = 0.009$). The most common adverse effects experienced by study participants in both groups were drowsiness and sedation (45.8 %), dizziness (42.2%), nausea and vomiting (32.5%). No patients experienced hallucinations or disorientation and only two experienced dysphoria, both in the placebo group. One patient in the ketamine group had a vivid dream [1.2%] (Table 2). The mean time of discharge for the ketamine group was 3.0 ± 0.4 days (range 3–5, median of 3.0 days) and

Table 2: Frequency of the side effects observed between ketamine and placebo groups

Side Effects	Group Assigned		Total	*p*-value
	Ketamine	Placebo		
Respiratory depression	0	0	0	
	0%	0%	0%	
Urinary retention	0	0	0	
	0%	0%	0%	
PONV	15	12	27	0.44
	36.6%	28.6%	32.5%	
Dizziness	17	18	35	0.90
	41.5%	42.9%	42.2%	
Dysphoria	0	2	2	0.16
	0%	4.8%	2.4%	
Hallucinations	0	0	0	
	0%	0%	0%	
Drowsiness	18	20	38	0.73
	43.9%	47.6%	45.8%	
Pruritus	5	3	8	0.44
	12.2%	7.1%	9.6%	
Ileus/Constipation	0	2	2	0.16
	0%	4.8%	2.4%	
Diplopia	5	1	6	0.084
	12.2%	2.4%	7.2%	
Dreams	1	0	1	0.31
	2.4%	0%	1.2%	
Disorientation	0	0	0	
	0%	0%	0%	

PONV = Postoperative nausea and vomiting

for the placebo group 3.1 ± 0.4 days (range 2–5, median 3.0 days).

In both groups, about half the patients rated their pain management as 'very good'. None of the patients felt that pain was managed poorly. More of the patients in the ketamine group thought their pain control was very good (53% *vs* 39%) to excellent [25% *vs* 12%] ($p = 0.039$).

DISCUSSION

There is substantial evidence to support the co-administration of ketamine with an opiate to reduce the amount of opiate required for optimal pain relief and to lower the incidence of side effects of the latter (7–9, 12–13). This study showed that patients undergoing elective gynaecological surgery at the UHWI who received ketamine 0.15 mg/kg pre-induction did not require significantly less opioid than the placebo group nor were their pain scores improved. The lack of significant difference in these two outcomes is contrary to the findings of two studies that used a similar dosing regime: Rebecca *et al* in patients undergoing laparoscopic gynaecological surgery (8) and Roytblat *et al* after subcostal incision for open cholecystectomy (17). Tissue injury is likely to be more limited in these latter groups of patients, which may account for the difference in results. Other reports that have demonstrated improved analgesia with pre-incision ketamine have studied patients undergoing ambulatory (18) or minimally invasive arthroscopic surgery (6) which have similar post-

operative pain requirements. In a study done by Karaman *et al*, patients who had total abdominal hysterectomy received ketamine 0.4 mg/kg either pre or post abdominal incision and no improvement in pain scores or morphine consumption was seen in either group (19). The small dose of ketamine had the clear advantage of reducing side effects (6, 7). The lack of difference in this study may have also resulted from the scheduled, traditional dosing regimen used routinely postoperatively at the UHWI which limited variation of dosing according to severity of pain.

Menigaux *et al* (5) reported no benefit of ketamine administration on pain scores at rest when ketamine 0.15 mg/kg was given before surgical incision or postoperatively. However, significant pain relief on movement was obtained in both ketamine-treated groups during the first physical therapy session. This study did not assess pain scores with movement which may explain the lack of significant difference in pain scores.

In this study, in spite of no difference in analgesic consumption between groups, more patients in the ketamine group thought their pain management was very good to excellent, 77.9% *vs* 51.2% ($p = 0.039$). Patients were blinded, which would have eliminated patient bias due to expectation of better analgesia. This anomaly could be related to the psychotropic effects of ketamine (20), resulting in an overall better perception of their analgesic management. In addition, the validity of the testing tool could be questioned. Only one question on overall satisfaction was used, when a series of questions designed to elicit their opinion on whether doses were administered regularly, if they had to request analgesia, and if so, if it was then administered promptly, could have given a more comprehensive picture of satisfaction.

Sedation is a significant side effect of both opioid and ketamine use. In this study, a significant difference was observed in the level of sedation two hours postoperatively between the ketamine and placebo groups ($p = 0.009$) where the ketamine group was less sedated. This is difficult to explain, especially in light of the fact that opioid consumption was not decreased. However, for the other time periods, no significant difference was observed. Zakine *et al* (21) also did not observe any significant changes in sedation scores for patients who received a ketamine bolus dose followed by an infusion intra or perioperatively *versus* the control. In this study, the incidence of postoperative nausea and vomiting was not statistically different between the ketamine and placebo groups (37% and 29%, respectively), probably related to the lack of an opioid–sparing effect.

Sub-anaesthetic doses (0.1–0.5 mg/kg) of ketamine impair some domains of cognitive function, such as attention, free recall, recognition memory and thought processes in healthy human volunteers (22, 23). Other studies have shown that analgesic doses of ketamine (*ie* 100–500 μg/kg) alter mood states and produce dose-related impairment of sensory perception or the process of sensory integration (22–24). Perceptual and mood changes at larger doses of ketamine (*eg* 500 μg/kg) have been shown to resemble some aspects of schizophrenia and/or psychosis, including hallucinations, vivid dreams, confusion and dysphoria (20, 22). None of the patients experienced hallucinations or disorientation and only two experienced dysphoria, both in the placebo group. One patient who received ketamine had a vivid dream. There was no difference in time to hospital discharge between both groups, most likely because there was no difference in the incidence and severity of side effects.

During the study period, postoperative pethidine was consistently prescribed at 100 mg intramuscularly every six hours regardless of the patient's weight and type of surgery. However, pethidine was only administered if the patient complained, and the six-hour dosing was often exceeded, but rarely given more frequently. This irregular dosing can result in significant falls in the plasma concentration of pethidine, and therefore cause patients to be in severe pain and discomfort. Administration of pethidine should be to prevent pain rather than in response to pain. The fact that pethidine was not administered appropriately may have resulted in a disconnect between the consumption of analgesia and the need for analgesia. Further work, incorporating the use of PCA pumps that would eliminate the impact of "prn" administration of analgesics on the ward, is required to resolve this observation. It will take consistent education to dispel the fears and negative attitudes concerning narcotics and so optimize postoperative pain management at the UHWI.

Inter-observer bias was possible, as there were several interviewers. Gynaecological patients were given morphine intra-operatively and in the PACU, but pethidine on the ward. In order to compare total postoperative opioid requirements, the morphine equivalent pethidine dose had to be determined, which may have introduced errors. The anaesthetist was not blinded because of safety concerns and this could have introduced bias.

In summary, ketamine 0.15 mg/kg given pre-induction did not significantly reduce postoperative narcotic requirements or pain intensity, nor did it increase the incidence of adverse effects. Despite this, more patients who received ketamine reported higher levels of satisfaction with their pain management. Further studies could include assessing the effect of a higher dosage of ketamine such as 0.4 mg/kg and also the effect of timing of the dose. We recommend that pain assessment scales be used routinely to assess patients in the PACU and on the wards, and be clearly documented on the patients' chart. Audits on postoperative analgesic prescribing practices and actual administration are needed to determine if opioids need to be administered on a more regular basis. The establishment of acute pain teams at our institution should be considered to optimize postoperative analgesia.

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