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# Evaluation of the Effectiveness of Intra-Operative Low Dose Ketamine Infusion on Post-Operative Pain Management Following Major Abdominal Gynaecological Surgeries

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**Abstract**

**Background**: Post-operative pain management has remained a major challenge to most surgeons and patients despite the availability of an array of pharmacologically active agents and techniques. The multimodal approach to post-operative pain management is the current trend in achieving better post-operative analgesia with minimal or no side-effects. The pharmacology of ketamine, its availability, accessibility, cost effectiveness and relative minimal side-effects at low doses, make ketamine a good option in the management of post-operative pain especially in low resource countries like Nigeria.

**Aim**: The aim of the study was to determine the effectiveness of continuous intra-operative infusion of low dose of ketamine at 0.5mg/kg/hr on post operative analgesia following major abdominal gynaecological surgeries

**Materials & Methods**: The study was a prospective, double blinded, and randomized controlled trial carried out in ESUT Teaching Hospital, Enugu following ethical approval by the hospital Ethics Committee. The participants were randomized into two groups: A &B. Group A (fentanyl-ketamine group) received continuous intravenous infusion of 2µg/kg/hr of fentanyl + 0.5mg/kg/hr of ketamine whereas group B (fentanyl-normal saline group) received intravenous infusion of 2µg/kg/hr of fentanyl + normal saline only. All patients had standard monitoring of the blood pressure, oxygen saturation, ECG, end tidal carbon dioxide and temperature peri-operatively. The primary outcome measure was time to first request for analgesia after surgery. Secondary outcome measures were pain scores in the first six and at the twenty fourth hours, post-operative analgesic consumption and the overall satisfaction with pain control. Pain scores were assessed using the numerical rating scale.

**Data analysis**: Data obtained from the study was analyzed using statistical package for social sciences version 22. The data was summarized using proportions, means, and standard deviation and the results presented in tables. Inter-group comparison was done with chi-square test for categorical variables and students t-test for continuous variables. A p-value of less than 0.05 was considered statistically significant.

**Results**: The two groups were compatible with respect to socio-demographic characteristics, duration of surgery and the doses of fentanyl administered intra-operatively. The time to request for analgesia was longer and statistically significant for the ketamine-normal saline group, 71.69±4.54 minutes as against the fentanyl-ketamine group, 33.97±5.28 minutes

(t=32.062, p<0.001). Both groups had NRS less than 3 within the first 6 hours post surgery. The NRS pain assessment in the first 6 hours at rest and at deep inspiration showed no statistically significant difference. The worst pain 24 hours was not statistically significant either. The post-operative analgesic (morphine) consumption was lower for fentanyl-ketamine group at all measured points from the 1st to the 24th hour of post-operative period. The reduction in morphine consumption was also statistically significant from the first hour to the 24th hour of post-operative period in the fentanyl-ketamine group. The level of satisfaction with overall pain control was better in the ketamine group (p<0.001). There was no observed statistically significant undesirable effect or complication in either group

**Conclusion**: The administration of intra-operative low dose ketamine infusion with fentanyl to patients during major abdominal gynaecological surgeries enhanced post-operative analgesia and overall satisfaction with pain control. It reduced post-operative analgesic requirements in the immediate post-operative period. There were no significant side-effects or complications.

**Key words**: Evaluation, Effectiveness, intra-operative, low-dose ketamine, post-operative pain management



## Introduction

Post-operative pain is undesirable in all surgical procedures and adequate pain relief during the immediate post operative period is essential for early resumption of normal activities.[1] Unrelieved post-operative pain may result in clinical and psychological changes that may increase morbidity and mortality as well as cost and may decrease the quality of life afterwards.[2] Advances in the knowledge and varied modes of management of intra-operative and post-operative pains improve patient outcome during surgery. Despite this improvement many patients still suffer from pain after surgery.[3] This is probably due to difficulties in balancing an effective peri-operative pain treatment regime with acceptable side-effects. The efficacy of management of severe peri-operative pain with strong opiods is well documented.[1] The relative inaccessibility and periodic non-availability of opiods in many health institutions and centres in Nigeria has limited its use. Poor governmental policies, unwholesome organizational structures and its erratic supply to recognized institutions are major barriers to accessibility of opiods in Nigeria.[4] Also the fear of common side-effects associated with the use of opiods like respiratory depression, limit the judicious use of opiods by many prescribers.[5]

Regional anaesthetic techniques are documented alternatives for controlling peri-operative pain.[1] However, the skill and equipments required for such regional techniques are not readily available in Nigeria and other resource-poor countries, hence, the low incidence of their use.[6] Considerations for the under treatment of post-operative pain and the limitation of opiod monotherapy made Kehlet et al [5] in 1993 to develop multimodal analgesic therapy to improve analgesic efficacy and reduce side-effects. The concept employs the use of combination of analgesics which act additively or synergistically to produce better pain relief with the use of lower doses of each drug thereby reducing side-effects.[5] Advances have been made in countries where the pool of drugs to choose from is wide; drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), clonidine, acetominophen, gabapentin, local analgesic agents for wound infiltration and regional nerve blocks have been employed as adjuncts to opiods and found to reduce opiod consumption by 20-40% and opiod

related side-effects by 30%.[7]The NSAIDs have peripheral analgesic effects via the inhibition of the cyclo-oxygenase pathway by preventing the production of prostaglandins, thromboxanes and prostacyclins. There is a ceiling effect to the dose-response curve of NSAIDs. This means that after a therapeutic ceiling is achieved increasing the dose increases the side-effects without any additional analgesia. But their serial side-effects such as mucosal erosion, platelets inhibition, bleeding tendencies in susceptible individuals are well documented.[7]Adjuncts like clonidine may cause allergic reactions presenting with hives, difficult breathing and facial, lips, tongue and throat edema. Other common side-effects may include tremors, drowsiness, dizziness, irritability, dyspnoea on mild exertion and confusion.

Renewed interest in ketamine as an analgesic drug was rekindled because of its N-methyl-D-aspartate (NMDA) receptor antagonist effect, with the potential to prevent 'wind up' and spinal cord sensitization.[8]When combined with opiods intra or post-operatively, its ability to enhance analgesic effects and reduce analgesic requirements while limiting the supposed side-effects have been shown.[9]This is achieved via a low dose of the synergetic drugs as compared to when either is used solely, although some studies on ketamine are contradictory.[10]

However, considering the mechanism of action of ketamine as an NMDA receptor blocker and the plurality of the nature of the pain pathway, ketamine could be a fruitful therapy for improving post-operative pain and opiod effectiveness. The effects of low dose ketamine administered on the post-operative pain varies depending on the dosing of the drugs.[11]These could be pre-incisional, intra-operative, continuous infusion and post-operative administration via infusion or the combination of the different methods. Pain is a personal and subjective experience that involves sensory, emotional and behavioural factors associated with actual or potential tissue damage or described in terms f such damage.[12]Pain is considered the 5$^{th}$ vital sign and of utmost importance in the management of patients. There is still significant post-operative pain in many countries and regions of the world. In their questionnaire based prospective study in about three hundred USA hospitals involving 500 hundred adults it was found that 77% of adult patients reported pain after surgery with 80% of these experiencing moderate to severe pain, despite an organized pain management program or structure in 46% of the hospitals.[13]Also, Soyannwo and Faponle found that about 50% of patients have experienced severe pain in the course of their management post-operatively.[3]In the UK, based on a level-1 evidence work done by Dolin et al, the incidence of post-operative pain in relation to the mode of analgesic administration showed intramuscular administration: 67% moderate and 29% severe pain; intravenous patient controlled analgesia (PCA): 36% moderate and 10% severe pain; while epidural had the least pain occurrence of 21% and 8% for moderate and severe pain respectively. On the overall, assuming a mixture of analgesic techniques the incidence of post-operative pain was put at 41%.[14]In a survey of 5703 surgical patients in Canada via a phone call 24 hours post ambulatory surgery, 30% had moderate to severe pain 24 hours after surgery.[15]Despiteall theimprovement in the technique of analgesic administration, no centre has reached the UK audit commission's standard of less than 5% of patients experiencing severe pain after major surgery[16]hence the need for this study.

**Aim**: The aim of this study was to determine the effectiveness of continuous intra-operative infusion of low dose ketamine on management of post-operative pain following major abdominal gynaecological surgeries.

**Objectives**: The specific objectives were to determine:

1. The duration of post-operative analgesia following intra-operative infusion of low dose ketamine
2. The total dose and frequency of analgesic requirement in the first 6 hours post surgery
3. The quality of post-operative analgesia following intra-operative infusion of low dose ketamine
4. Patient's satisfaction with analgesia in the immediate post-operative period

**Null hypothesis**: Intra-operative infusion of low dose ketamine will not enhance pot-operative pain management

**Alternate hypothesis**: Intra-operative low dose ketamine infusion will enhance post-operative pain management

**Study Area**: The study was done in ESUTH Enugu, a tertiary hospital in the capital of Enugu State, south-East, Nigeria. The centre serves as a training centre for undergraduates and resident doctors. It also receives referrals from all the surrounding states of Abia, Ebonyi, Imo and Anambra

**Materials & Methods**:

This was a prospective, double- blinded, randomized study involving 2 groups: A & B. Following approval from the hospital ethics committee, informed consent from the patient and permission from the consultants in-charge of the patient, those randomized in to Group A received intra-operative infusion of **2µ/kg/hr** of fentanyl + **0.5mg/kg/hr** of ketamine; whereas group B received **2µ/kg/hr** fentanyl + normal saline. The patient's weight and height were noted and they were taught to use Numerical Rating Scale (NRS) before the surgery. The medications were prepared by a neutral assistant who is not involved in the study, properly labeled A or B and stored in a designated refrigerator where the anaesthestist on duty will access it during surgery and administer without knowing the medication. The drugs were prepared in a 50ml syringe with normal saline to ensure blinding by a consultant anaesthetist without any knowledge or input from the principal investigator.

All the patients had intravenous access established with size 16-gauge cannular in both hands. Hypnosis was achieved with sleep dose of thiopentone or maximum dose of **5mg/kg** body weight. Muscle relaxant for intubation was achieved with pancurorium **0.1kg/ml** and throughout the procedure. Patients were connected to the anaesthetic machine and ventilated manually or connected to the ventilator. They were maintained on isoflurane (inhalational agent) in oxygen via a cycle absorber breathing system throughout the procedure. This was regulated based on the haemodynamic demand of the patient.

Analgesic demands were maintained by using another intravenous access once patients were positioned, scrubbed and draped. That was the zero time. The regimes were as described earlier viz A or B. The drugs were applied via administered via (Graseby 3300) a syringe driver at a rate appropriate rate as indicated earlier. At the last stitch on the skin the inhalation al agent and anaesthetic infusion were turned off (end time). The residual intramuscular block were reversed anti-cholinestrase, neostigmine (2.5mg) and anti-cholinergic atropine 0.02mg/kg administered with or just before neostigmine. Patient was extubated on clinical establishment of adequate reversal of muscle relaxation. Patients were handed over to the attending nursing staff recovery room that was also blinded. Post-operative analgesia was administered using patient controlled analgesia infusion pump. PCA was commenced in the recovery room when patient's pain score is greater than 3 or patient requests for analgesia. PCA was used in the first 24 hours post surgery to ensure adequate analgesia and analgesic consumption recording for all patients. The PCA pump was programmed to deliver morphine at a basal infusion rate of 0.015mg/kg/hr or a bolus delivery of 2.5mg per dose on demand, with a lockout time of 20 minutes.

**Sampling method**: Randomization was done using block randomization method. Here the patients were randomized into a lock of 4 namely: AABB, ABBA, ABAB, BABA, BBAA and BAAB. The blocks were randomly chosen based on random numbers selected through an uninvolved party using random number generator on Microsoft Excel. Patients were then assigned either A or B based on the block combination selected via the random numbers by the uninvolved party.

**Sample size determination**: The sample size was calculated using the formula for detecting the difference between two means.[17]

$N=2[Z_1\alpha/2+Z_1\beta]^2/[\mu_0-\mu_1/\delta]^2$

Where N = sample size on each group

$Z\alpha$ = standard deviation of $\alpha$ = 1.96 at 5%

Zβ = standard deviation of β = 0.84 at 80%

$2[Z_1\alpha/2+Z_1\beta]^2$= 15.68, which can be rounded up to 16, producing the sample formula below: $16s^2/ ð^2+1$

Where s =standard deviation of time to first request for analgesia in the post-operative period from a previous study which is in the ketamine group.[18]

ð = assuming a minimum difference of 5 minutes in each time to first request for analgesia between ketamine and the control group.

N = 16x $(7^2/5^2)+1$ =32 participants required in each group

Sample size was increased by 10% to provide for attrition = 32+3 = 35

Hence, the minimum sample size for each group was 35 and 70 in all.

**Inclusion criteria**: The inclusion criteria included:

- Gynaecological patients between the ages of 18 to 65 years
- Booked obstetric and gynaecological patients under general anaesthesia
- American Society of Anaesthesiologist physical status 1 or 11

**Exclusion criteria**: These included:

- American Society of Anaesthesiologist physical status >2
- Mute patients or patients with impaired cognitive functions
- History of allergies to ketamine or fentanyl
- Psychiatric patients
- Patients who refused consent

**Data analysis**: Data obtained from the study was analyzed using statistical package for social sciences version 22. The data was summarized using proportions, means, and standard deviation and the results presented in tables. Inter-group comparison was done with chi-square test for categorical variables and students t-test for continuous variables. A p-value of less than 0.05 was considered statistically significant.

**Results**:

Seventy participants (35 in each group) were recruited in the study and they completed the study, hence there was no attrition. The two groups were comparable and similar with respect to age, weight, height and ASA physical status as shown in table 1 below.

**Table 1: Socio-demographic characteristics of the patients**

| Variables | Fentanyl-ketamine group | Fentanyl-normal saline group | $t/X^2$ | p-value |
|---|---|---|---|---|
| **Age** | | | | |
| **Mean ± SD** | **46±7.68** | **44.07±9.25** | **1.189** | **0.238** |
| **Weight** | | | | |
| **Mean ± SD** | **67.66±7.04** | **66.96±8.26** | **0.381** | **0.705** |
| **Height** | | | | |
| **Mean ± SD** | **1.64±0.06** | **1.59±0.08** | **2.647** | **0.010** |
| **Body mass index** | | | | |
| **Mean ± SD** | **25.22±2.57** | **26.21±2.75** | **1.558** | **0.124** |
| **ASA N(%)** | | | | |
| **I** | **28(80.0)** | **30(85.7)** | **0.402** | **0.526** |
| **II** | **7(20.0)** | **5(14.3)** | | |

The mean time to the first request for analgesic was prolonged in the ketamine group and the difference was statistically significant. For the ketamine group the mean time was 71.69±4.54minutes compared with the control group with 33.97±5.28 minutes (t =32.062, p<0.001) as shown in table 2 below.

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**Table 2: Mean time to first request for analgesia (TFA)**

| TFA from intubation | Fentanyl-ketamine | Fentanyl-normal saline | T | p-value |
|---|---|---|---|---|
| Mean±SD (Min) | 71.69±4.54 | 33.97±5.28 | 32.062 | >0.001 |

The NRS pain assessment in the first 6 hours at rest and at deep inspiration showed that the patients in the ketamine group were more associated with lower pain scores than patients in the control group ($x^2$ = 13.333, p = 0.001) as shown in table 3 below. Majority of the patients in the ketamine group (94%) had lower pain score (1-2) when compared to the control group with higher pain scores (2-3).

**Table 3: Pain scores (NRS) in the first 6 hours during normal respiration**

| NRS (TFA) | Fentanyl-ketamine | Fentanyl-normal saline | $X^2$ | p-value |
|---|---|---|---|---|
| 1 | 8(22.9) | 0(0.0) | 13.333 | 0.001 |
| 2 | 25(1.4) | 25(71.4) | | |
| 3 | 2(5.7) | 10(28.6) | | |

However, the worst pain scores were not significantly different between the 2 groups ($\mathbf{x^2 = 1.067, p = 0.587}$) as shown in table 4 below.

**Table 4: Pain score (NRS) at the 24th hour post surgery (worst pain)**

| NRS in 24 hours | Fentanyl-Ketamine (%) | Fentanyl-normal saline (%) | $X^2$ | p-value |
|---|---|---|---|---|
| 1 | 1(2.9) | 0(0.0) | 1.067 | 0.587 |
| 2 | 27(77.1) | 27(77.1) | | |
| 3 | 7(20.9) | 8(22.9) | | |

The cumulative morphine consumption in the ketamine group was lower than that recorded for the control at all measured points in the 24 hours post-operatively. The morphine consumption became statistically significant from the first hour to the 24th hour with the p-value of 0.001 as shown in table 5 below.

**Table 5: post-operative morphine consumption**

| Mean amount of morphine consumed (mg) | | | | |
|---|---|---|---|---|
| Post-op time(hrs) | Fentanyl-ketamine (mean±SD) | Fentanyl-normal saline(mean±SD) | t | p-value |
| 1 | 1.02±0.11 | 3.32±0.44 | 29.822 | <0.001 |
| 2 | 2.03±0.21 | 4.50±0.23 | 46.344 | <0.001 |
| 3 | 3.05±0.32 | 5.49±0.36 | 30.290 | <0.001 |
| 4 | 4.08±0.42 | 6.48±0.49 | 22.100 | <0.001 |
| 5 | 5.09±0.52 | 7.48±0.59 | 17.756 | <0.001 |
| 6 | 6.55±1.29 | 8.76±1.09 | 7.719 | <0.001 |

| | | | | |
|---|---|---|---|---|
| **24** | **24.93±5.34** | **25.59±2.97** | **0.648** | **<0.001** |

From the table 6 below, 22.9%of the ketamine group requested for extra analgesia from the PCA machine in the 6th hour while 51.4% of the control demanded for extra analgesia from the PCA machine once or twice. This was statistically significant ($x^2$ = 7.662. p=0.022). Similarly, 40% of the ketamine group demanded for extra analgesia in 24 hours as against 68.5% of the control (**$x^2$ = 8.458, p = 0.037**) as shown in table 6 below.

**Table 6: PCA Machine demand**

| **Number of good demand in 6 hours** | **Fentanyl-ketamine** | **Fentanyl-normal saline** | **$X^2$** | **p-value** |
|---|---|---|---|---|
| **0** | **27(77.1)** | **17(48.6)** | **7.662** | **0.022** |
| **1** | **7(20.0)** | **11(31.4)** | | |
| **2** | **1(2.9)** | **7(20.0)** | | |
| **Number of good demand in 24 hours** | **Fentanyl-ketamine** | **Fentanyl-normal saline** | **$X^2$** | **p-value** |
| **0** | **21(60.0)** | **11(31.4)** | **8.458** | **0.037** |
| **1** | **8(22.9)** | **7(20.0)** | | |
| **2** | **4(11.4)** | **11(31.4)** | | |
| **3** | **2(5.7)** | **6(17.1)** | | |

The results also showed that the ketamine group was 8 times more satisfied with the analgesia given than the control (p<0.001, OR = 8.346, 95% CI = 2.857-24.379) as shown in table 7.

**Table 7: Patient satisfaction with pain control at 24th hour**

| **Variables** | **Fentanyl-ketamine n(%)** | **Fentanyl-normal saline n(%)** | **p-value** | **OR** | **CI** |
|---|---|---|---|---|---|
| **Very satisfied** | **26(74.3)** | **9(25.7)** | **<0.001** | **8.346-2.857** | **24.379** |
| **Satisfied** | **9(25.7)** | **26(74.3)** | | | |

Three patients each from both group had nausea and vomiting post-operatively as shown in table 8 below, but this was not statistically significant.

**Table 8: Observed complications/side-effects**

| **Complications/side-effects** | **Fentanyl-ketamine N(%)** | **Fentanyl-normal saline N(%)** | **$X^2$** | **p-value** |
|---|---|---|---|---|
| **Nil** | **32(91.4)** | **32(91.4)** | **0.000** | **1.000** |
| **Nausea/vomiting** | **3(8.6)** | **3(8.6)** | | |

**Discussion**:

The aim of this study was to determine the effectiveness of continuous intra-operative infusion of low dose ketamine on management of post-operative pain following major abdominal gynaecological surgeries. At the end, it revealed that when ketamine is used as adjuvant with fentanyl intra-operatively there is significant prolongation of the first request for analgesia post-operatively and hence, a good technique for post-operative pain management. This agrees with the findings by Roytblat eta al.[19]This was also another randomized trial like ours with results corroborating each other. Another randomized trial in which ketamine was given pre- and post-incision revealed that ketamine given before incision in the first group resulted in prolongation

of time to first request for analgesia when compared with the pre-incision group.[20]The study differed somewhat from our study in which ketamine was given as an infusion intra-operatively but with similar outcome. This showed that ketamine as an adjunct to general anaesthesia will help to control post-operative pain irrespective of the regime employed. When compared with a rather not too similar study in which ketamine was given intra-operatively to the two groups, but was replaced with morphine post-operatively in one of the groups, ketamine group still showed a better post-operative pain control.[21]This further reinforces the idea that ketamine could be a preferred drug for post-operative pain management in major abdominal surgeries. The improved analgesic effects of low dose ketamine was also supported by many other studies.[22-25]However, in the study by Edward et al, the post-operative pain control was not improved or reduction in morphine consumptionnoticed when <4μ/kg/min of ketamine without a loading dose among 40 patients who had abdominal surgeries.[26]The difference could have arisen from the variation in number of participants, dose of the drug used in each study and the population studied. While our study involved 70 participants randomized into 2 groups, the quoted study above recruited 40 patients randomized into 4. The dose of ketamine used in our study was 0.5mg/kg/hr whereas the quoted study used a lower dose. The population studied in that study was entirely old people while we studied a combination of both old and young. All these could have explained the dissimilarities observed. Patient's satisfaction with overall pain control was significantly improved among the ketamine group in our study. This was opposed the finding of Kim et al which could not demonstrate any difference.[27]Adverse effects such as dizziness, blurred vision, diplopia, itching, urinary retention and excessive salivation were not significantly observed in both arms. This agrees with the finding by Sethna et al who also concluded that the side-effects when ketamine is given in low doses were essentially the same with patients who had opiods only.[28]The small but equal proportion of patients on each arm that had nausea/vomiting suggested that it was probably due to the opiod administered.

**Conclusion**: The administration of intra-operative low dose ketamine infusion with fentanyl to patients during major abdominal gynaecological surgeries enhanced post-operative analgesia and overall satisfaction with pain control. It reduced post-operative analgesic requirements in the immediate post-operative period. There were no significant side-effects or complications.

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