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Effect of intraoperative low-dose ketamine infusion on postoperative pain management following mastectomy

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Abstract

Background: The multimodal approach to postoperative pain management is the current trend of achieving adequate postoperative analgesia with minimal or no side effects of analgesic drugs. We sought to determine the effect of continuous intra-operative infusion of low–dose ketamine on post-operative analgesia following mastectomy.

Methods: The study was a prospective, double blind, randomized controlled study. The patients were randomized into either: (a) FK group, which received intravenous continuous infusion of 2 µg/kg/hr of fentanyl + 0.5 mg/kg/hr of ketamine. Or (b) FN group, which received intravenous continuous infusion of 2 µg/kg/hr of fentanyl and normal saline. The primary outcome was time to first request for analgesia after surgery. Secondary outcomes were pain scores in the first twenty-four hours, postoperative analgesic consumption and overall satisfaction with pain control.

Results: The time to first request for analgesia was longer in the ketamine group 245.61± 160.46 minutes versus 179.42 ± 161.46 minutes in the control group (p=0.0217). The median NRS in the first 6 hours showed no significant difference. The cumulative postoperative tramadol consumption in the ketamine group was lower than that recorded for the control group (162.73±60.43mg versus 182.95±63.27mg). The satisfaction with overall pain control was better in the ketamine group (p=0.030).

Conclusion: The administration of intraoperative low dose ketamine infusion with fentanyl to patients during mastectomy enhances postoperative analgesia and overall satisfaction with pain control. It reduces postoperative analgesic requirement in the immediate postoperative period with minimal side effect.

Keywords: *Postoperative pain; multimodal analgesia; ketamine; mastectomy*

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Résumé

Contexte: L'approche multimodale de la gestion de la douleur postopératoire est la tendance actuelle à obtenir une analgésie postopératoire adéquate avec des effets secondaires minimes ou inexistants des analgésiques. Nous avons cherché à déterminer l'effet de la perfusion intraopératoire continue de kétamine à faible dose sur l'analgésie postopératoire après mastectomie.

Méthodes: L'étude était une étude prospective, double aveugle, randomisée et contrôlée. Les patients ont été randomisés dans l'un ou l'autre: (a) groupe FK, qui a reçu une perfusion intraveineuse continue de 2 µg / kg / h de fentanyl + 0,5 mg / kg / h de kétamine. Ou (b) groupe FN, qui a reçu une perfusion intraveineuse continue de 2 µg / kg / h de fentanyl et de solution saline normale. Le critère de jugement principal était le moment de la première demande d'analgésie après la chirurgie. Les critères de jugement secondaires étaient les scores de douleur au cours des vingt-quatre premières heures, la consommation d'analgésiques postopératoires et la satisfaction globale à l'égard du contrôle de la douleur.

Résultats: Le temps à la première demande d'analgésie était plus long dans le groupe kétamine 245,61 ± 160,46 minutes contre 179,42 ± 161,46 minutes dans le groupe témoin (p = 0,0217). NRS médian au cours des 6 premières heures n'a montré aucune différence significative. La consommation cumulée de tramadol postopératoire dans le groupe kétamine était inférieure à celle enregistrée pour le groupe témoin (162,73 ± 60,43 mg contre 182,95 ± 63,27 mg). La satisfaction à l'égard du contrôle global de la douleur était meilleure dans le groupe kétamine (p = 0,030).

Conclusion: L'administration d'une perfusion peropératoire de kétamine à faible dose avec du fentanyl chez des patients pendant une mastectomie améliore l'analgésie postopératoire et la satisfaction globale du contrôle de la douleur. Elle réduit les besoins analgésiques postopératoires dans la période postopératoire immédiate avec un effet secondaire minimal.

Mots clés: *douleur postopératoire; analgésie multimodale; la kétamine; mastectomie*

Introduction

Adequate post-operative pain relief is needed for early resumption of normal activity after surgery and is a valued humanitarian service [1]. It will reduce the length of hospital stay, improve convalescence period, and decrease morbidity [1].

Advances in the knowledge and varied mode of management of intraoperative and postoperative pain has improved patients' outcome following surgery. Despite this improvement, many patients still suffer from pain after surgery [2-3]. This is probably due to difficulties in balancing an effective peri-operative pain treatment regimen with acceptable side effects. The efficacy of strong opioids in the management of severe peri-operative pain is well documented [1], however the periodic non-availability and relative inaccessibility of opioids to many health practitioners and centres in Nigeria has limited its use.

Consideration for the multifaceted nature of pain mechanism and pathways, and the complications associated with opioid monotherapy made Kehlet et al [4] in 1989 to develop multimodal analgesic therapy to improve analgesic efficacy and reduce side effects. This is particularly important following mastectomy in view of the complex innervation of the breast leading to considerable acute postoperative pain and a high risk of developing chronic pain if poorly treated [5]. The breast derives its innervation from the anterior and lateral branches of the second to the sixth intercostal, the anterior branch of the lateral cutaneous branch of the fourth thoracic nerve, the supraclavicular nerve, which is a branch of superficial cervical plexus and the intercostobrachial nerve, which is a branch of the second thoracic nerve.

Ketamine became an analgesic drug of interest because of its N-methyl-D-aspartate (NMDA) receptor antagonist effect, with the potential to prevent "wind up" and prevent spinal cord sensitization [6,7]. When combined with opioids intra or post operatively, its ability to enhance analgesic effect and reduce analgesic requirement while limiting the supposed side effect has been shown [8-10]. This is achieved via the lower doses of the synergistic drugs as compared to when either is used solely, although some studies on ketamine are in the contrary [11,12]. The aim of this study was to determine the effect of continuous intra-operative infusion of low–dose ketamine (analgesic dose) on post-operative pain management following mastectomy.

Methods

Following the local ethical committee approval and informed consent obtained, 68 female patients above 18 years and less than 65years of age, undergoing elective simple or modified radical mastectomy surgery and classified as ASA I or II were randomly distributed into the two study groups.

Routine work up for surgery was done and all patients were investigated as required. Standard pre-operative fast was prescribed and pre-medication given based on the patient's pre-morbid condition. All patients received 5mg diazepam orally on the morning of surgery, IV metoclopramide 10mg and IV 4mg dexamethasone at induction as anti-emetic. The patients were taught to use the Numerical Rating Scale (NRS) preoperatively to assess pain and pain relief postoperatively.

Study medications were prepared in advance and same were given to the blinded investigator or duty anaesthetist. Patients were recruited into either of the two groups:

1. Study drug group (FK): 2μg/kg/hr of fentanyl + 0.5mg/kg/hr of ketamine.
2. Control group (FN): 2μg/kg/hr of fentanyl.

Drug preparations were made up to equal volumes in a 50ml syringe with 0.9% Saline to ensure blinding. Standard monitoring with pulse oximetry, non-invasive blood pressure measurement, electrocardiography, end-tidal carbon dioxide and temperature were employed. General anaesthesia was performed using sodium thiopentone as induction agent. Muscle relaxation and maintenance was achieved with pancuronium. Suxamethonium was used to facilitate endotracheal intubation when indicated. Halothane in 100% oxygen was used throughout the procedure and was titrated to haemodynamic parameters.

Study medications were commenced using another intravenous access once the patients were positioned, scrubbed and draped i.e. zero time. The regimes were either (1) fentanyl-ketamine infusion as the study drug group or (2) fentanyl-normal saline infusion as the control group. The drugs were administered via a syringe driver (Graseby 3300). At the last stitch on the skin, the inhalational agent and the analgesic infusion (study or control drug) were turned off i.e. end time. The residual neuromuscular block was reversed with standard dose of neostigmine (2.5mg) and atropine (1.2mg). Patients wereextubated and transferred to PACU on clinical establishment of adequate muscle reversal i.e. head lifting for five seconds, spontaneous eye opening or a sustained hand grip.

Monitoring in the PACU was guided by the Aldrete scoring system, NRS for pain and Ramsay sedation score. Side effects like nausea and vomiting were managed appropriately.

Postoperative analgesic drug was administered using the patient (PCA) infusion pump

(Graseby 3300) and commenced when patient's pain score (NRS) is greater than 3 or patient requested for analgesia. PCA was used in the first 24hours post-surgery to ensure adequate analgesia and analgesic consumption recordings for all patients. The PCA pump was programmed to deliver tramadol at a basal infusion rate of 0.1mg/kg/hr. Boluses delivery of 2.5mg per dose on demand, with a lockout time of 20minutes. (As at the time of conducting this study, parenteral morphine was not available in Nigeria).

Measurements

The patient's demographic data and preoperative haemodynamic variables were obtained. Intraoperatively, the patient's arterial blood pressure (systolic, diastolic and mean) were measured by automated non-invasive blood pressure monitor, electrocardiogram to monitor cardiac activity and arterial oxygen saturation ($Sp0_2$) using pulse oximeter were recorded at intervals of 5 minutes throughout the course of surgery and anaesthesia.

Postoperatively, time of first postoperative analgesic request was noted. Pain intensity was measured using the NRS immediately on arrival in PACU by the investigator, then at every 30minutes interval till the sixth hour post-operatively. The total amount of tramadol consumed in the postoperative period was also recorded. Level of sedation was assessed using Ramsay sedation score. Side effects or undesirable experiences were noted e.g. awareness under anaesthesia, hallucination, nightmares, nausea, vomiting, and abnormal movements. Patients' mood, satisfaction with pain control and overall satisfaction were all assessed at the twenty-fourth hour using the American Pain Society Patient Outcome Questionnaire for acute and chronic pain [13].

Protocol for the management of undesirable effect was as follows:

a) Shivering – low dose tramadol 10mg intravenously (bolus)
b) Postoperative nausea/vomiting – 10mg IV metoclopramide + 4mg IV dexamethasone. If recalcitrant IV Ondansetron 400mg stat was given.

Data analysis

Data obtained from the study were subjected to statistical analysis using Statistical Package for Social Sciences (SPSS) 22.0, Chicago IL. Data was summarized using proportion, mean and standard deviation. Intergroup comparisons were done with categorical variables compared using the chi-square test or Fisher's exact test where appropriate, while continuous variables were compared using the student t-test or Mann-Whitney U test where appropriate. Repeated measure ANOVA was done to assess any statistically different in the change in anaesthetic demand levels over time between both groups. A p-value of less than 0.05 was considered as significant.

Results

Sixty-six of the recruited patients completed the study while one patient in each group could not complete the study. The two groups were comparable with respect to socio-demographic characteristics. (Tables 1).

Table 1: Socio-demographic characteristics of the patients

Variable		FK	FN	P-value
Age (years)				
mean ±SD		44.70 ± 10.58	45.06 ± 9.64	0.884
Weight (Kg)				
mean ±SD		66.21 ± 15.03	69.66 ± 18.47	0.409
Height (metres)				
mean ±SD		1.60 ± 0.06	1.64 ± 0.048	0.206
Body Mass Index kg/m²				
mean ±SD		25.30 ± 4.78	24.43 ± 9.89	0.844
ASA N (%)	**I**	21 (31.8%)	23 (34.8%)	0.602
	II	12 (18.2%)	10 (15.2%)	

Pain assessment and analgesic consumption

The mean time to first request for analgesic (TFA) was significantly prolonged in the ketamine group. The mean values were 245.61±160.46 (CI=190.86-300.35) minutes for the ketamine group compared with the control group with 179.42±161.46

(CI=124.34-234.52) minutes (p=0.021). The values were within 95% confidence interval (Table 2).

Table 2: Time to first request of analgesia, pain score at 1st request of analgesia and within the 1st g hour of normal rhythmic respiration

Variable	FK	FN	P-Valve
TFA from last stitch mean ± SD (min)	245.61±160.46	179.42 ±161.42	0.021*
Intraoperative fentanyl consumption (µg)	424.91±159.77	444.87±215.62	0.671
Numerical rating scale at first request Median(range)	4(2-5)	3(1-8)	1.000
Pain score (NRS) on arrival in PACU Median(range)	0(0-1)	0(0-6)	0.183
30 minMedian(range)	0(0-2)	0(0-5)	0.145
1 hourMedian(range)	0(0-4)	0(0-6)	0.366
2 hours Median(range)	0(0-3)	0(0-7)	0.241
4 hoursMedian(range)	0(0-3)	0(0-6)	0.314
6 hours Median(range)	0(0-2)	0(0-5)	0.102

Table 3: Postoperative Tramadol Consumption

Mean amount of tramadol consumed (mg) Post operativetime	FK mean ± SD	FN mean ± SD	P-value[#]
1 hour	0.47±1.88	1.64±3.63	0.124
2 hours	3.45±6.74	11.79±34.07	0.108
3 hours	7.37±10.97	19.36±34.05	0.013*
4 hours	13.09±14.96	21.59±16.12	0.033*
5 hours	20.43±18.77	29.80±19.89	0.049*
6 hours	28.20±21.89	38.78±22.51	0.053
24 hours	162.73±60.43	182.95±63.27	0.119

#: Mann-Whitney U test
*p-value < 0.05

The median NRS pain score at first request of analgesia was 4(2-5) and 3(1-8) for ketamine and control group respectively (p=1.000). Though there was no statistical difference in pain scores, the ketamine group had the highest individual pain score. Both groups had very low NRS less than 3 within the first six hours post-surgery (Table 2). As shown in Table 3, the cumulative postoperative tramadol consumption in the ketamine group was lower than that recorded for the control group (162.73±60.43mg versus 182.95±63.27mg) and at all measured points in the first 24hours after surgery. The tramadol consumption became statistically significant from the third through to the fifth hour postoperative time, the p values being 0.013, 0.033 and 0.049 respectively.

Assessment of side effects

One patient in the ketamine group had hallucinatory experience. No patient complained of such in the control group. In the ketamine group, 7 (21.2%) patients had episodes of nausea or vomiting postoperatively, while 8 (24.2%) patients had similar experience among the patients who did not receive ketamine with fentanyl infusion. All the patients who had nausea or vomiting received intravenous 4 mg dexamethasone and 10 mg metoclopramide. However 1 patient had to receive a dose of ondansetron before the symptom could abate. No patient complained of awareness under anaesthesia.

Table 4: Side effects

Complication/ undesired side effect	FK n=33(%)	FN n=33(%)	Total n=66(%)	p-value
Awareness under anaesthesia	0 (0.00)	0 (0.00)	0 (0.00)	-
Delayed recovery	1 (3.03)	0 (0.00)	0 (0.00)	0.314
Hallucination	1 (3.03)	0 (0.00)	1 (1.50)	0.314
Nausea/Vomiting	7 (21.21)	8 (24.24)	15 (22.50)	0.761
Hypotension	1 (3.03)	1 (3.03)	2 (3.03)	1.000

Table 5: Patients' sedation parameters within the first 6 hours post-surgery

Variables	FK Median (range)	FN Median (range)	P-value
Ramsay sedation score			
0 min	3(2-5)	2(1-5)	0.038*
30 min	2(2-4)	2(1-4)	0.146
1 hour	2(2-3)	2(2-2)	0.079
2 hours	2(1-3)	2(2-2)	1.000
4 hours	2(2-3)	2(2-2)	0.317
6 hours	2(2-2)	2(2-2)	1.000

**p-value < 0.05*

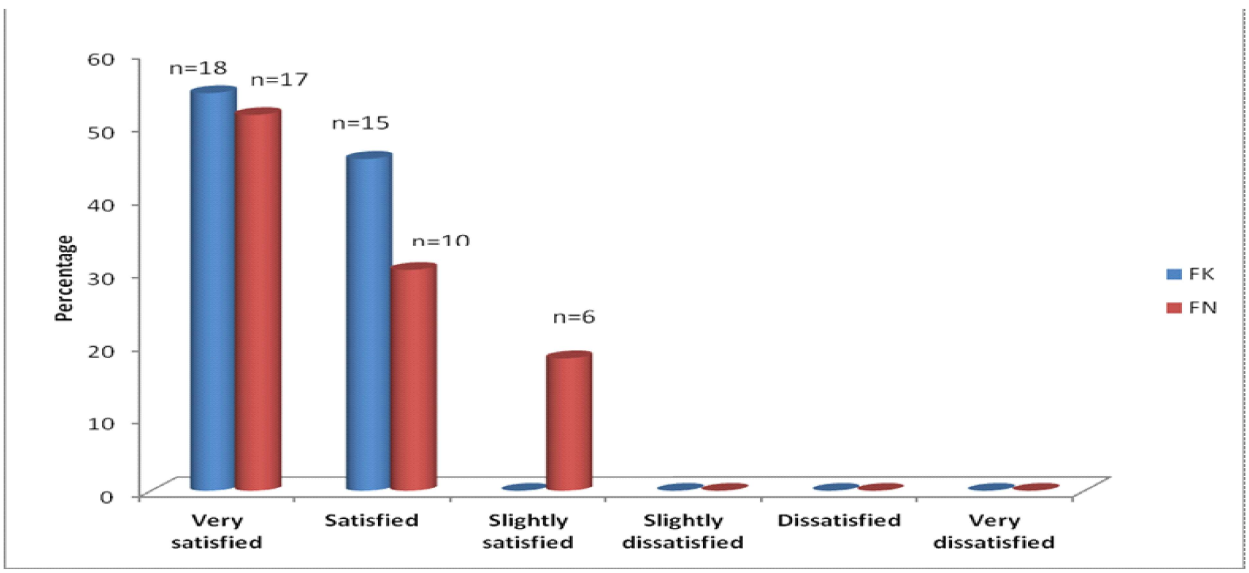

***Fig.1:** Patients' level of satisfaction with overall pain control*
P-value = 0.030
FK: Fentanyl-ketamine mixture group; FN: Fentanyl only group; n: Number of patients

Hypotension occurred in 1(3%) patient in each group necessitating switching off the inhalational agent, resuscitation with crystalloid and blood as appropriate intraoperatively. The patient in the ketamine groupwith hypotension had excessive blood loss (estimated at 2000mls) necessitating transfusion of 2 units of blood perioperatively. Nystagmus and undue or excessive muscular activity were not observed (Table 4). The Ramsay sedation score on arrival in PACU was significant (p=0.038), median (range) Ramsay sedation score for the ketamine group was 3(2-5) while those for those on fentanyl-only regimen was 2(1-5). Subsequently the statistics shows no difference in the two groups up till the 6th hour (Table 5).

Patient satisfaction with pain control

The patients' satisfaction with overall pain control was found to be statistically different (p=0.030). All the patients (100%) in the ketamine group were either satisfied or very satisfied with their analgesia during the study period. However, only twenty-seven (88%) patients in the control group were either satisfied or very satisfied with their analgesia. Six patients, accounting for 18.2%, were slightly satisfied with their pain relief. No patient in the two groups was dissatisfied with pain control (Figure 1).

Discussion

This study showed that when ketamine is used as an adjuvant with fentanyl intraoperatively, there is significant prolongation of the time to first request of analgesia postoperatively, compared to when only fentanyl is administered intra-operatively. Ketamine is a well-known general anaesthetic used in the last four decades; it is readily available and has short acting analgesic property. Its use is associated with varying degrees of psychomimetic side effects when used at higher doses of greater than 2 mg/kg IV or rapid intravenous administration of >40 mg/min [14]. Low-dose ketamine is defined as a bolus of less than 2 mg/kg given as an intramuscular injection or less than 1 mg/kg when administered via the intravenous or epidural route [15]. For continuous intravenous infusion, low-dose ketamine is defined as a rate of ≤20 µg/kg/min [15]. The present study employed ketamine at a dose of 0.5 mg/kg/hour which is equivalent to 8.3µg/kg/min.

Roytblat *et al* [16] demonstrated an increase in the time to first request for analgesia (TFA) in patients who had 0.15 mg/kg of ketamine in addition to fentanyl for intraoperative analgesia while undergoing cholecystectomy in contrast to those who had only fentanyl administered. The time difference in their study was about 10-35 minutes as against the 66 minutes in this study. The difference may be due to the single bolus dose technique employed in that study compared to a continuous ketamine intraoperative infusion employed in this study. This is in line with the hypothesis by Sabine and Marcel [17] that ketamine should be administered throughout the period of generation of high intensity nociception and inflammatory stimulation.This difference may also be due to the cumulative effect of ketamine administered during the period of mastectomy (73.12±34.32mg a" 1.1mg/kg) which is much more than what Roytblat *et al* administered (0.15mg/kg), though Roytblat *et al* administered the ketamine as a bolus before skin incision in contrast to this study with no loading dose before commencement of the infusion at skin incision.

The result of Guignard *et al* [18] is similar to ours, in which a low dose ketamine was used with supplementation of desflurane-remifentanil anaesthesia in a variety of patients who had colonic surgeries. They studied a total of 50 patients, with 25 in each arm of the study. They administered a loading dose of 0.15 mg/kg and thereafter continued with an infusion rate of 2 µg/kg/min in the treated arm. While maintaining desflurane at 0.5 minimum alveolar anaesthetic concentration without N_2O, a remifentanil infusion was titrated to autonomic response. The time to first request of analgesia was significantly prolonged in the ketamine group, with a p-value of <0.01.

Fu *et al* [19] administered a preemptive dose of 0.5 mg/kg of ketamine prior to surgical incision to patients going for abdominal surgeries, thereafter continuous infusion of 10 µg/kg/min until wound closure was completed. The second group had 0.5 mg/kg ketamine immediately after wound closure. The two groups in Fu's study received morphine as postoperative analgesia. The team observed a prolonged TFA time in the group that had continuous infusion of ketamine following a loading dose. This is similar to the results obtained by Roytblat *et al* [16] and this present study.

A pre-emptive study by Amanor-Boadu *et al* [20] in patients who had intra-abdominal gynaecological surgery, demonstrated significant prolongation of TFA time in the pre-incisional ketamine administered group compared to those with post-incisional ketamine. The post-incision group should have recorded a prolongation in TFA time provided the effect of the analgesia demonstrated was due to serum level of ketamine. The prolongation in time to first request for analgesia demonstrated was however not sustained beyond the immediate postoperative period.

Patients' satisfaction with overall pain control was in favour of patients who received ketamine intraoperatively. Unlike the work of Kim and colleague [21] which could not demonstrate any difference with regard to patient satisfaction in a study population of sixty patients who had elective spinal fusion. This could probably be due to the administration of ketamine at a lower rate of 1-2 µg/kg/min before skin incision to 48 hours after surgery in their study, against this study where ketamine was administered at the rate of 8.3µg/kg/min within the period of surgery.

Aside from the anaesthetic and analgesic property of ketamine, it also causes sedation when used. This effect was demonstrated in this study. Though the time to extubation after surgery from the last stitch was similar in both the FN and FK groups, there was a significant difference in the Ramsay sedation score in the ketamine-fentanyl group when compared with the group that had only intraoperative fentanyl on arrival in the PACU. However, by the 30th minute of arrival in the PACU the sedation score was similar. Results of researchers like Ilkjær *et al* [11], Guignard *et al* [18], Mathisen *et al* [22], and Subramaniam *et al* [23] also reported significant higher sedation amongst the ketamine treated groups.

Emergence phenomenon of ketamine which has limited its use was also examined in order to know its safety profile in this study. It was observed that there was no significant emergence reaction of low-dose ketamine infused at the rate of 8.3µg/kg/min in combination with fentanyl for patients who had general anaesthesia. Vivid and unpleasant nightmares or hallucination occurred during recovery and for up to 24 hours. Only one patient reported hallucinatory experience among the ketamine group in this study, this represents 3% of the treated population. The incidence of hallucinatory experience was put at 5-30% by White *et al* [24] after high dose ketamine anaesthesia. The factors identified to have affected emergence experience include age, sex, subjects who usually dream, high dose of ketamine >2mg/kg IV and rapid intravenous administration of ketamine >40mg/minute. Volunteers who received equi-analgesic doses of either racemic or S(+) ketamine reported less tiredness and impaired cognitive function [25].

Adverse effects like dizziness, blurred vision, diplopia, itching, urinary retention, and excessive salivation were not significantly different in both groups. This is in agreement with the report of Sethna *et al* [26] who also concluded that these side effects, when ketamine is given at low dose were essentially the same with patients who had opioids only.

Although the occurrence of nausea and vomiting was not statistically significant in the two groups in this present study, the percentage of patients who had nausea or/and vomiting was 22.7%, (21.2% for ketamine-fentanyl group and 24.2% for fentanyl only group). The use of opioid could have played a role in the higher incidence in the study group. The Cochrane analysis on perioperative ketamine for acute postoperative pain by Bell *et al* [27], showed a significant reduction in nausea and vomiting in ketamine treated patients having analysed a data from 705 patients treated with ketamine and 578 patients receiving control.

An important limitation of this study is that different cadres of surgeons were involved resulting in varying degree of duration of surgery and by inference also varying degrees of noxious stimuli.

Conclusion

Low dose ketamine when administered during general anaesthesia as a continuous infusion in addition to fentanyl compared with fentanyl only infusion, increases the duration of analgesia and reduces postoperative analgesic consumption and enhances patients' satisfaction about pain control with minimal side effects. The use of low dose ketamine as an adjunct should be considered as an effective technique in providing additional analgesia for patients undergoing mastectomy.

References

1. Rosenquist RW and Rosenberg J: Post-operative pain guidelines. Reg. Anaesth Pain Med 2003; 28:279- 288.
2. Soyannwo O.A. Postoperative pain control: prescription pattern and patients' experience. West Afr J Med 1999; 18:207-210.
3. Famewo C.E. Study of incidence of post-operative pain among Nigerian patients. Afr J Med sci 1985; 14:175-179.
4. Kehlet H and Dahl JB: The value of multimodal or balanced analgesia in postoperative treatment. AnesthAnalg 1993; 77: 1048-1056.
5. Bartakke AA and Varma MK. ATOWT 403-Analgesia for Breast Surgery- A Brief Overview(30 April 2019) http://www.wfsahq.org/resources/anaesthesia-tutorial-of-the-week. Accessed 25th October 2019.
6. Oye I, Paulsen O and Maurset A. Effects of ketamine on sensory perception: Evidence for a role of N-methyl-D-aspartate receptors. J Pharmacol ExpTher 1992; 260:1209-1213.
7. Arendt-Nielsen L, Nielsen J, Petersen-Felix S, Schnider TW and Zbinden AM. Effect of racemic mixture and the (S+) isomer of ketamine on temporal and spatial summation of pain. Br J Anaesth 1996; 77:625-631.
8. Menigaux C, Guignard B, Fletcher D, *et al.* Intraoperative small-dose ketamine enhances analgesia after outpatient knee arthroscopy. AnesthAnalg 2001; 93:606-612.
9. Kwok RF, Lim J, Chan MT, Gin T and Chiu WK. Preoperative ketamine improves postoperative

analgesia after gynaecologic laparoscopic surgery. AnesthAnalg 2004; 98:1044–1049.
10. Stubhaug A, Breivik H, Eide PK, Kreunen M and Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. ActaAnaesthesiolScand 1997; 41:1124–1132.
11. Ilkjær S, Nikolajsen L, Hansen TM, *et al.* Effect of i.v. ketamine in combination with epidural bupivacaine or epidural morphine on postoperative pain and wound tenderness after renal surgery. Br J Anaesth 1998; 81:707–712.
12. Dahl V, Ernoe PE, Steen T, Raeder JC and White PF. Does ketamine have pre-emptive effects in women undergoing abdominal hysterectomy procedures.AnesthAnalg 2000; 90:1419–1422.
13. Gordon DB, Polomono R, Pellino TA, *et al.* Psychometrics of the Revised American Pain Society Patient Outcome Questionnaire (APS-POQ) for Quality Improvement of Acute and Cancer Pain Management.Journal of Pain 2010; 11(11):1172-1186.
14. White PF, Way WL and Trevor AJ. Ketamine: its pharmacology and therapeutic uses. Anesthesiology 1982; 56: 119-136.
15. Schmid RL, Sandler AN and Katz J: Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain 1999; 82:111-125.
16. Roytblat L, Korotkoruchko A, Katz J, *et al.* Postoperative pain: the effect of low dose ketamine in addition to general anaesthesia. Anesth Analg 1993;77:1161-1165.
17. Sabine Himmelseher and Marcel E. Durieux: Ketamine for Perioperative Pain Management. Anesthesiology 2005; 102:211-220.
18. Guignard B, Coste C, Costes H *et al*. Supplementing Desflurane-Remifentanil anesthesia with small-dose ketamine reduces perioperative opioid analgesic requirements. AnesthAnalg 2002; 95:103-108.
19. Fu ES, Miguel R and Scharf JE. Preemptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery. AnesthAnalg 1997; 84:1086-1090.
20. Amanor-Boadu SD, Sanusi AA, Arowojolu AO and Abdullahi AA. Ketamine for preemptive analgesia in major gynaecologic surgery. The Nigerian Journal of Surgical Research 2003; 5 (1-2):7-11.
21. Kim HS, Kim SI, Young OK S *et al*. Opioid sparing effect of low dose ketamine in patients with intravenous patient-controlled analgesia using fentanyl after lumbar spinal fusion surgery. Korean J Anesthesiol 2013; 64(6):524-528.
22. Mathisen L, AasbØ V and Raeder J. Lack of pre-emptive analgesic effect of (R)- ketamine in laparoscopic cholecystectomy. Acta Anaesthesiol Scand 1999; 43:220-224.
23. Subramaniam B, Subramaniam k, Pawar DK and Sennaraj B. Preoperative epidural ketamine in combination with morphine does not have a clinically relevant intra-and postoperative opioid sparing effect. AnesthAnalg 2001; 93:1321-1326.
24. White PF, Way WL and Trevor AJ. Ketamine: its pharmacology and therapeutic uses. Anesthesiology 1982; 56: 119-136.
25. Pfenninger EG, Durieux ME and Himmelseher S: Cognitive impairment after small-dose ketamine isomers in comparison to equianalgesic racemic ketamine in human volunteers. Anesthesiology 2002; 96:357–366.
26. Sethna NF, Liu M, Gracely R, Bennett GJ and Max MB. Analgesic and cognitive effects of intravenous ketamine-alfentanil combinations versus either drug alone after intradermal capsaicin in normal subjects. AnesthAnalg 1998; 86:1250-1256.
27. Bell RF, Dahl JB, Moore RA and Kalso EA. Perioperative ketamine for acute postoperative pain (Review). The Cochrane Library 2010, Issue 11.

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