Comparison of pregabalin versus ketamine in postoperative pain management in breast cancer surgery

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ABSTRACT

Background: Breast surgery compromises one of the most common cancer surgeries in females and commonly followed by acute postoperative pain. Pregabalin and ketamine have been used in many previous studies and was found to have a good analgesic profile. We assumed that pregabalin and ketamine can be used in control of postoperative pain in female patients undergoing breast cancer surgery. **Material and Methods:** Ninety female patients scheduled for cancer breast surgery were allocated in three groups (30 patients each), control group (group c) received preoperative placebo, pregabalin group (group p) received oral 150 mg pregabalin 1 h before surgery, ketamine group (group k) received intravenous (IV) 0.5 mg/kg ketamine with induction of anesthesia followed by 0.25 mg/kg/h IV throughout the surgery. All patients received general anesthesia and after recovery, the three groups were assessed in the first postoperative 24 h for postoperative visual analog scale (VAS) , total 24 h morphine consumption, incidence of postoperative nausea and vomiting (PONV), sedation score >2 and any complications from the drugs used in the study. **Results:** The use of pregabalin or ketamine was found to reduce total postoperative morphine consumption with $P < 0.001$. There was no difference between pregabalin and ketamine groups in opioid requirement. There was no difference between the three groups in postoperative VAS scores or incidence of PONV and sedation score >2. **Conclusion:** The use of preoperative oral 150 mg pregabalin 1 h before surgery or IV 0.5 mg ketamine with induction of anesthesia can reduce postoperative opioid consumption in breast cancer surgery without change in sedation or PONV and with a good safety profile.

Key words: *Breast cancer surgery, ketamine, postoperative pain, preemptive, pregabalin*

INTRODUCTION

Undermanaged postoperative pain increases the incidence of deep venous thrombosis, pulmonary embolism, myocardial infarction, pneumonia, and poor wound healing. These effects increase postoperative morbidity and mortality, and decreases patient satisfaction.[1]

Gabapentinoids (gabapentin and pregabalin) were first used as anti-epileptics but later on found to have anti-nociceptive effects. Pregabalin-a structural analog to gamma-amino butyric acid which is an inhibitory neurotransmitter-has a better pharmacokinetic profile than gabapentin as it has more bioavailability (90%) and more rapid absorption reaching its peak level after 1 h. Pregabalin has linear dose-dependent plasma concentration level in contrast to gabapentin.[2] Pregabalin half-life is 4.6-6.8 h,[3] in addition, pregabalin has no hepatic metabolism and has less drug interaction than gabapentin. Pregabalin has been used in many studies for control of postoperative pain and was found to have a good analgesic profile.[4-7]

N-methyl-D-aspartate (NMDA)-receptors have an important role in the pathophysiology of pain as they are responsible for central sensitization and wind-up phenomenon. Ketamine, as an NMDA receptor antagonist, has been studied for control of postoperative pain, but the results were contradictory. Some studies proved the preemptive analgesic effect of low-dose ketamine,[8,9] while others could not confirm this effect.[10-12]

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Pregabalin and ketamine have been used in comparison in one study done by Martinez *et al.* in patients undergoing total hip arthroplasty,[13] but they were not used before in breast surgery.

In our study, we assumed that preoperative administration of pregabalin or ketamine can control postoperative pain. We did this study to evaluate this assumption and to compare the analgesic profile of preoperative pregabalin with ketamine in patients undergoing breast surgery.

MATERIALS AND METHODS

After obtaining approval from the Local Ethics Committee and written informed consent from the patients, we studied 90 female patients with cancer breast, undergoing elective modified radical mastectomy. This study was done at National Cancer Institute — Cairo University. Patients, who were classified as American Society of Anesthesiologists physical status I and II with age between 18 and 65 years, were included in the study. Exclusion criteria were contraindications for ketamine, pregabalin or morphine use, severe cardiac, renal or hepatic diseases, preoperative use of corticosteroids and/or opioids, history of seizures disorders, daily use of analgesics, inability to use the patient-controlled analgesia (PCA) device and communication difficulties. A prospective, randomized, double-blind design was used, with both patients and postoperative assessors blinded to intraoperative management. All these patients were evaluated preoperatively for fitness of anesthesia. During the preanesthetic assessment, patients were instructed how to use the PCA device, and how to report pain on the 11-point visual analog scale (VAS). Patients were assigned to one of three groups of 30 patients each using a computer-generated random number assignment.

Control group: (group c)

Received a placebo capsule orally 1 h before induction of anesthesia and 5 ml normal saline intravenous (IV) before induction of anesthesia followed by saline infusion till the end of the surgery (the end of skin closure).

Pregabalin group: (group p)

Received a 150 mg pregabalin capsule orally 1 h before induction of anesthesia and 5 ml normal saline IV before induction of anesthesia, followed by saline infusion till the end of the surgery (the end of skin closure).

Ketamine group: (group k)

Received a placebo capsule orally 1 h before induction of anesthesia and 0.5 mg/kg ketamine in 5 ml of normal saline syringe IV before induction of anesthesia, followed by ketamine infusion at a rate of 0.25 mg/kg/h till the end of the surgery (the end of skin closure).

An anesthesiologist not related to the management of the patient or study prepared the drugs of the study according to randomization. The patients and the staff involved in data collection and patient management were unaware of the group assignment. Allocations were concealed in sequentially numbered sealed opaque envelopes, which were opened the day before surgery after patients had consented to the trial.

The anesthetic protocol was similar to all patients. Before the induction of anesthesia, hemodynamic variables such as mean arterial pressure and heart rate (HR) were recorded as baseline measurements. IV access was established, and patients were premedicated with 2 mg midazolam.

After preoxygenation with 100% oxygen, general anesthesia was induced with fentanyl 1-2 μg/kg IV, propofol 2 mg/kg IV, and atracurium 0.5 mg/kg IV anesthesia was maintained with oxygen 50% in air and sevoflurane 2-2.5%. Supplemental boluses of atracurium 0.1 mg/kg IV were administered as required to maintain muscle relaxation during surgery. Additional doses of fentanyl were given so as to maintain HR within 15% of the baseline value and systolic arterial blood pressure within 20% of the baseline value. The tidal volume was set at 8-10 ml/kg and respiratory rate was adjusted to maintain end-tidal CO_2 between 30 and 35 mmHg. Intraoperative monitoring included electrocardiography, arterial pressure, pulse oximetry, nasopharyngeal temperature, peripheral nerve stimulator, end-tidal CO_2 concentration, and urine output. At the end of surgery, muscle relaxation was reversed by IV neostigmine 0.05 mg/kg and atropine 0.01 mg/kg and then the extubation was done when the patients were fully awake.

After emergence from anesthesia, the patients were transferred to the recovery room, a PCA device was connected to the IV route of the patient. A solution of morphine (1 mg/ml) was prepared for the PCA. The PCA device was set to all groups with a demand dose of 1 ml and a lockout interval of 10 min and without a continuous background infusion,[14] then patients were assessed for the following parameters:

1. Visual analog scale (VAS) was used to assess the intensity of pain in patients after 30 min and subsequently after 2, 4, 6, 12, and 24 h after the emergence from anesthesia both at rest and on shoulder movement.
2. Total PCA morphine consumed by the patients in the first postoperative 24 h.
3. Sedation was assessed in the first postoperative 24 h by a 4-point scale.[15]

0 — awake and alert, 1 — mildly sedated, 2 — moderately sedated, aroused by shaking, 3 — deeply sedated, difficult to arouse even by shaking.

4. Any complications or side effects as postoperative nausea and vomiting (PONV), dizziness, visual disturbance, nightmares, and hallucinations were recorded up to 24 h after the surgery.

Sample size estimation

Sample size estimation was based on the study done by Kumar *et al.*[4] which found a mean score of VAS after 6 postoperative hours 4.12 ± 1.16 for oral pregabalin versus 5.8 ± 1.08 for placebo and also the study done by Singh *et al.*[16] which found a mean score of VAS after 6 h 3.65 for ketamine IV versus 4.4 for placebo. The primary outcome was VAS score after 6 postoperative hours, largest difference in VAS score to be detected was 2.15, within group standard deviation (SD) was 1.16 and effect size (difference/SD) was 1.8534. Sample size was estimated according to these mentioned parameters and the previous two studies with a significance of ($\alpha = 0.05$) and power ($1-\beta = 0.80$). The estimated minimum sample size required per group was six subjects. But to increase the power of the test (analysis of variance), we included 30 subjects per group to have a total of 90 subjects recruited and randomized equally into three study groups.

Statistical analysis

Statistical Package for Social Sciences, Inc.,Chicago, III.,USA version 17.0 was used for statistical analysis. Mean ± SD was used for description of VAS scores and total 24 h morphine consumption. Analysis of variance test was used to compare means of the three study groups. *P* values were set significant at 0.05 levels.

RESULTS

The results of the present study revealed no significant difference between the three groups as regard demographic data [Table 1].

There was no significant difference in VAS scores between the three groups either at rest or with shoulder movement at all-time intervals. This is shown in Tables 2 and 3.

The use of preoperative oral 150 mg pregabalin resulted in significant reduction of total postoperative 24 h morphine consumption in group (p) which was (20.23 ± 6.8 mg) as compared to that of placebo in group (c) which was (34.43 ± 10.14 mg) and $P < 0.001$. Furthermore, the use of IV ketamine 0.5 mg/kg with induction resulted in significant decrease in postoperative 24 h morphine consumption in group (k) which was (23.10 ± 6.91 mg) as compared to that of placebo and $P < 0.001$. There was no significant difference between pregabalin group (p) and ketamine group (k) in the amount of 24 h morphine consumption.

Table 1: Demographic data in both groups

Demographic data	Group (c) (*n* = 30)	Group (p) (*n* = 30)	Group (k) (*n* = 30)	*P*
Age (years)	53.87±8.09	53.47±7.44	53.10±6.22	0.92
Weight (kg)	74.57±10.01	73.90±8.97	72.93±7.89	0.78
Height (cm)	161.60±5.60	164.20±5.28	162.43±4.56	0.14
Duration of surgery (min)	123.17±15.06	125.00±17.32	122.50±15.47	0.82

Values are (mean ± SD). **P* value is significant ≤0.05. Group (c): Control placebo group, Group (p): Pregabalin group, Group (k): Ketamine group, SD: Standard deviation

Table 2: Visual analog scale at rest

VAS-R	Group (c) (*n* = 30)	Group (p) (*n* = 30)	Group (k) (*n* = 30)	*P*
VAS-R 30 min	4.53±1.074	4.37±0.89	4.33±0.661	0.64
VAS-R 2 h	4.63±1.098	4.33±1.124	4.67±0.992	0.49
VAS-R 4 h	4.37±1.033	4.13±1.008	4.27±0.691	0.48
VAS-R 6 h	4.20±1.064	3.97±1.066	4.17±0.913	0.67
VAS-R 12 h	3.80±0.961	3.73±1.172	3.70±1.022	0.89
VAS-R 24 h	3.00±1.114	2.90±1.155	2.93±1.015	0.93

Values are (mean ± SD). **P* value is significant ≤0.05. VAS-R: Visual analog scale at rest; Group (c): Control placebo group; Group (p): Pregabalin group, Group (k): Ketamine group, SD: Standard deviation

Table 3: Visual analog scores with movement

VAS-M	Group (c) (*n* = 30)	Group (p) (*n* = 30)	Group (k) (*n* = 30)	*P*
VAS-M 30 min	6.83±1.085	6.47±1.008	6.20±1.270	0.16
VAS-M 2 h	6.37±0.964	6.20±1.243	6.03±1.033	0.47
VAS-M 4 h	6.23±0.858	6.07±1.048	6.17±1.020	0.77
VAS-M 6 h	5.90±1.029	5.57±0.935	5.70±1.088	0.36
VAS-M 12 h	5.07±0.944	4.87±0.819	4.93±0785	0.84
VAS-M 24 h	4.33±1.093	4.00±1.083	4.23±1.040	0.41

Values are (mean ± SD). **P* value is significant ≤0.05. VAS-M: Visual analog scale with movement, Group (c): Control placebo group, Group (p): Pregabalin group, Group (k): Ketamine group, SD: Standard deviation

The incidence of a sedation score >2 was similar between the three groups in the first 24 h which was 0 patients in both placebo and ketamine groups and only 1 patient in the pregabalin group. Furthermore, there was no significant difference in the incidence of PONV in the first postoperative 24 h which was 6, 5, and 6 patients in the placebo, pregabalin and ketamine groups, respectively. Other complications as dizziness, visual disturbance, nightmares, and hallucinations were not recorded by any of the patients included in this study during the first 24 h of the postoperative period.

DISCUSSION

Neither the use of preoperative IV ketamine 0.5 mg/kg nor the preoperative oral use of 150 mg pregabalin could reduce VAS scores in patients undergoing breast cancer surgery, but they were proven in this study to reduce postoperative

opioid requirements rendering them a good co-analgesic in multi-modal analgesia with a good safety profile.

Absence of significant difference in VAS scores between the three groups may increase the validity of decreased opioid consumption in both ketamine and pregabalin groups in spite of achieving equal pain relief.

This study failed to detect difference between the use of low dose ketamine with induction of anesthesia and the use of preoperative oral 150 mg pregabalin 1 h before surgery in the decrease of postoperative requirement, but this could not be generalized to population. If we took the amount of postoperative opioid requirement as a primary outcome, and if the study done by Martinez *et al*.[13] on pregabalin and ketamine was taken as a reference in postoperative opioid requirement, the estimated total sample size should be 330 patients with 110 patients in each group. Hence, sample size in our study was not large enough to detect this difference.

Excitatory neurotransmitters as glutamate are released in response to nociceptive impulses coming from nociceptive C fibers which are stimulated in response to prolonged stimulation from tissue damage. These excitatory neurotransmitters activate the postsynaptic NMDA receptors resulting in wind-up phenomenon, central sensitization, and central nervous system hypersensitivity. This cascade can magnify the postoperative pain.[16] NMDA antagonists as ketamine and gabapentinoids as pregabalin produce their analgesic action by inhibiting the hyperexcitability of dorsal horn neurones resulting from tissue damage, so they can decrease the intensity of acute postoperative pain. This is unlike the mechanism of action of other traditional analgesics which inhibit the afferent input impulses from both intact and traumatized tissues.[17]

There was a strong conflict about the efficiency of the use of preoperative pregabalin in control of postoperative pain. Pregabalin was first used as an effective preemptive analgesic in dental surgery in a study done by Hill *et al*. in 2001. The study showed that pregabalin reduced postoperative pain intensity.[7] In another study done by Reuben *et al*., pregabalin decreased postoperative opioid consumption in patients undergoing spinal fusion surgery when it was administered preoperatively in a dose of 150 mg and repeated after 12 h.[6] Jokela *et al*., found that administration of 300 mg pregabalin twice daily decreased the postoperative oxycodone consumption in patients scheduled for laparoscopic hysterectomy.[5] Preoperative dose of 150 mg pregabalin was found to decrease postoperative pain scores and total use of postoperative fentanyl and diclofenac in the first 6 h postoperatively in patients undergoing lumbar laminectomy.[4] All these studies were with the good analgesic efficacy of preoperative pregabalin.

However, other studies were against these previous results. Paech *et al*. found that preoperative oral dose of pregabalin of 100 mg failed to decrease pain intensity in patients undergoing minor gynecological operations,[18] taking into consideration the smaller dose of pregabalin and minimal pain intensity in this type of surgeries, the difference in results could be explained.

In a study done by Bornemann-Cimenti *et al*., they found that administration of preoperative 300 mg pregabalin resulted in a reduction of postoperative opioid consumption but did not change pain scores in patients undergoing transperitoneal nephrectomy.[19] They found no change in PONV, no difference in sedation nor pregabalin side effects. These results were similar to our results.

Our results were also in agreement with a meta-analysis done in 2011 by Zhang *et al*. They demonstrated that preoperative administration of pregabalin can reduce the first 24 h postoperative opioid consumption, but cannot reduce pain scores although the individual studies in this meta-analysis showed significant less pain scores in patients receiving pregabalin rather than patients receiving placebo.[20]

Some studies showed that low dose ketamine can reduce VAS scores and postoperative opioid consumption if given preoperatively in pregnant women undergoing cesarean section.[9,21] However, other authors found that ketamine did not produce that effect in the same type of surgery.[10-12]

In abdominal surgery, ketamine was found to reduce pain intensity and postoperative opioid consumption in a dose of 0.5 mg/kg.[8,22] Laskowski *et al*. demonstrated that ketamine was more effective in preemptive analgesia in surgeries with high VAS scores in which there was more tissue damage and with more extensive surgeries as thoracotomy and upper abdominal surgery while these results differed with less painful surgeries as lower abdominal surgeries.[23]

Ketamine has been used before in breast surgery in a study done by Adam *et al*. They found that a small dose of ketamine (0.15 mg/kg) failed to prove a preemptive analgesic effect. The opposition of these results compared to ours can be explained by their use of a very low dose of ketamine (0.15 mg/kg).[24]

The use of both pregabalin and ketamine in preemptive analgesia was studied recently by Martinez *et al*. they found that combined oral pregabalin (150 mg) and IV ketamine (0.5 mg/kg) can effectively reduce postoperative opioid requirement. They also found that ketamine alone or pregabalin alone decreased postoperative morphine consumption compared to placebo. These results are in

agreement with our results. Martinez *et al*. also found that there was no difference in pain scores in patients receiving ketamine nor pregabalin in comparison to patients who received placebo in hip arthroplasty surgery, and this is consistent with our results.[13]

One of the limitations in our study is the short duration of postoperative assessment which could not evaluate the effect of ketamine or pregabalin in reduction of chronic pain. It is well-known that pregabalin is a good analgesic used in the treatment of chronic neuropathic pain. Another limitation is the relatively small sample size which rendered the study not powerful enough to detect the difference in side effects of pregabalin or ketamine or the difference between pregabalin and ketamine in reduction of postoperative opioid consumption. Hence, we recommend larger sample size in future results.

REFERENCES

1. Carr DB, Goudas LC. Acute pain. Lancet 1999;353:2051-8.
2. Gajraj NM. Pregabalin: Its pharmacology and use in pain management. Anesth Analg 2007;105:1805-15.
3. Frampton JE, Foster RH. Pregabalin: In the treatment of postherpetic neuralgia. Drugs 2005;65:111-8.
4. Kumar KP, Kulkarni DK, Gurajala I, Gopinath R. Pregabalin versus tramadol for postoperative pain management in patients undergoing lumbar laminectomy: A randomized, double-blinded, placebo-controlled study. J Pain Res 2013;6:471-8.
5. Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. Pain 2008;134:106-12.
6. Reuben SS, Buvanendran A, Kroin JS, Raghunathan K. The analgesic efficacy of celecoxib, pregabalin, and their combination for spinal fusion surgery. Anesth Analg 2006;103:1271-7.
7. Hill CM, Balkenohl M, Thomas DW, Walker R, Mathé H, Murray G. Pregabalin in patients with postoperative dental pain. Eur J Pain 2001;5:119-24.
8. Behdad A, Hosseinpour M, Khorasani P. Preemptive use of ketamine on post operative pain of appendectomy. Korean J Pain 2011;24:137-40.
9. Menkiti ID, Desalu I, Kushimo OT. Low-dose intravenous ketamine improves postoperative analgesia after caesarean delivery with spinal bupivacaine in African parturients. Int J Obstet Anesth 2012;21:217-21.
10. Han SY, Jin HC, Yang WD, Lee JH, Cho SH, Chae WS, *et al*. The Effect of low-dose Ketamine on post-caesarean delivery analgesia after spinal anesthesia. Korean J Pain 2013;26:270-6.
11. Bauchat JR, Higgins N, Wojciechowski KG, McCarthy RJ, Toledo P, Wong CA. Low-dose ketamine with multimodal postcesarean delivery analgesia: A randomized controlled trial. Int J Obstet Anesth 2011;20:3-9.
12. Reza FM, Zahra F, Esmaeel F, Hossein A. Preemptive analgesic effect of ketamine in patients undergoing elective cesarean section. Clin J Pain 2010;26:223-6.
13. Martinez V, Cymerman A, Ben Ammar S, Fiaud JF, Rapon C, Poindessous F, *et al*. The analgesic efficiency of combined pregabalin and ketamine for total hip arthroplasty: A randomised, double-blind, controlled study. Anesthesia 2014;69:46-52.
14. Howell PR, Gambling DR, Pavy T, McMorland G, Douglas MJ. Patient-controlled analgesia following caesarean section under general anesthesia: A comparison of fentanyl with morphine. Can J Anaesth 1995;42:41-5.
15. Chia YY, Liu K, Liu YC, Chang HC, Wong CS. Adding ketamine in a multimodal patient-controlled epidural regimen reduces postoperative pain and analgesic consumption. Anesth Analg 1998;86:1245-9.
16. Singh H, Kundra S, Singh RM, Grewal A, Kaul TK, Sood D. Preemptive analgesia with Ketamine for Laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol 2013;29:478-84.
17. Mathiesen O, Jacobsen LS, Holm HE, Randall S, Adamiec-Malmstroem L, Graungaard BK, *et al*. Pregabalin and dexamethasone for postoperative pain control: A randomized controlled study in hip arthroplasty. Br J Anaesth 2008;101:535-41.
18. Paech MJ, Goy R, Chua S, Scott K, Christmas T, Doherty DA. A randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor gynecological surgery. Anesth Analg 2007;105:1449-53.
19. Bornemann-Cimenti H, Lederer AJ, Wejbora M, Michaeli K, Kern-Pirsch C, Archan S, *et al*. Preoperative pregabalin administration significantly reduces postoperative opioid consumption and mechanical hyperalgesia after transperitoneal nephrectomy. Br J Anaesth 2012;108:845-9.
20. Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: A meta-analysis. Br J Anaesth 2011;106:454-62.
21. Ngan Kee WD, Khaw KS, Ma ML, Mainland PA, Gin T. Postoperative analgesic requirement after cesarean section: A comparison of anesthetic induction with ketamine or thiopental. Anesth Analg 1997;85:1294-8.
22. Fu ES, Miguel R, Scharf JE. Preemptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery. Anesth Analg 1997;84:1086-90.
23. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth 2011;58:911-23.
24. Adam F, Libier M, Oszustowicz T, Lefebvre D, Beal J, Meynadier J Preoperative small-dose ketamine has no preemptive analgesic effect in patients undergoing total mastectomy. Anesth Analg 1999;89:444-7.

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