Comparative Research between Modified Pectoral Nerve Block with Adding Ketamine to Pubivacaine versus Modified Pectoral Nerve Block with Pubivacaine in Patients Undergoing Modified Radical Mastectomy

Noha Mohammed Khodary [*], Samia Yahey El Baradie , Ehab Hanafy Gendy , Mahmoud Ahmed Kamel

Article History: Received: 03.06.2023 Revised: 06.07.2023 Accepted: 10.07.2023

Abstract

Background: Pectoral nerve blocks (PECNB) have been demonstrated to deliver adequate analgesia and reduce opioid dose following modified radical mastectomy (MRM). The pain associated with peripheral neuropathy and spinal cord injury and persistent phantom limb pain may be relieved by low-dose intravenous (IV) ketamine (KET). The purpose of this research is to evaluate the effectiveness as well as safety of ultrasound guided (US) modified PECNB with Bupivacaine (BVC) and KET in comparison to BVC alone in patients having MRM for pain relief.

Methods: This prospective randomized single blinded clinical research was carried out in the National Cancer Institute (NCI) on adult females 20 to 60 years old, BMI of 25 – 40 kg/m^2 and ASA scoring system: ASAI and ASAII suffering from breast cancer arranged for MRM. Cases were divided into two equal comparable groups: group I received US modified ECNB with BVC and group II received US- modified PECNB with BVC plus KET.

Results: There was no statistically meaningful variation between the groups concerning intraoperative heart rate (HR), mean arterial pressure (MAP) and peripheral oxygen saturation ($SpO_{2)}$. Visual analogue scale (VAS) was significantly less in group II versus I at 12h postoperatively (P value <0.001) and was insignificantly different at 0.5, 6, 18 and 24h postoperatively. Time of 1st rescue analgesia was significantly delayed at group II versus I (P value <0.001). Total morphine requirements were significantly less in group II versus I (P value <0.001)**.** Incidence of postoperative nausea and vomiting (PONV) was 10 (12.05%) cases in group I and 2 (2.41%) cases in group II. PONV was significantly less in group II versus I (P value =0.002).

Conclusions: Patient discomfort, total opioid dosage, and PONV were all decreased when Ketamine was added to US modified Pectoral nerve block with Bupivacaine for MRM.

Keywords: Modified pectoral nerve block, modified radical mastectomy, Ketamine, Bupivacaine

* Anesthesia and Pain Management Department, National Cancer Institute, Cairo University, Cairo, Egypt

Introduction:

Significant pain occurs post-surgery even in relatively modest breast operation [1]. A modified radical mastectomy (MRM) is a popular surgical procedure in many cancer centers. There are physical and social implications to inadequate postoperative pain control. Through decreasing the surgery related physical burdens and the need for general anesthetics (GA) and analgesics, efficient acute pain management can help maintain the immune function [2].

MRM under GA requires the administration of morphine at dosage of 6 to 48mg [3], exposing cases to the risk of opioid-induced adverse reactions [4]. Acute postoperative pain is a significant risk factor for post MRM pain. Regional anesthesia procedures have improved the efficacy of acute pain management, leading to a reduction in chronic pain [5].

It has been shown that pectoral nerve blocks (PECNB) provide satisfactory analgesia after MRM and reduce opioid dose [6]. The objective of the PECNB is to inject local anesthesia into the interfacial space between the pectoralis major and minor muscles. A second variant of the PECNB is known as PECNB type II or modified PECNB. It is intended to obstruct the pectoral nerves, intercosto-brachial, intercostals (III, IV, V, and VI), and long thoracic nerve. During MRM, these nerves must be obstructed to secure complete pain control.

The PECNB II is constructed to anesthetize anterior upper latter chest area including overlying skin and breast through lateral branches of intercostal nerves [7, 8].

The N-methyl-D-aspartate (NMDA) receptor blocker ketamine (KET) acts in a non-competitive fashion. It's essential as a sedative, induction, and maintenance stages of general anesthesia. It has been noted that KET has anesthetic and pain-relieving effects on a systemic, regional, and local level [9].

KET reduces postoperative pain intensity for up to 48 hours, reduces cumulative 24-hour morphine dose, and delays the onset of the first call for rescue

analgesia [10]. It also enhances analgesia in cancer pain that is resistant to opioid therapy, but dysphoria and sedation are common [11].

Further research is needed to determine whether KET's mechanism of action is in the spinal cord or at higher locations [12], but it's clear that KET plays a part in preventing Opioid hyparalgesia (OIH). Low-dose intravenous KET appears to alleviate pain associated with peripheral neuropathy and spinal cord injury and persistent phantom limb pain in cases with chronic pain [13].

Studies comparing ultrasound (US)- modified PECNB with BVC and KET to US- modified PECNB with Bupivacaine BVC alone for analgesia in cases having MRM are the focus of this present research.

Patients and Methods:

This prospective randomized single blinded clinical research was carried out in the National Cancer Institute (NCI) on adult females 20 to 60 years old, BMI of 25 – 40 kg/m^2 and he American Society of Anesthesiologists (ASA) scoring system: ASAI and ASAII suffering from breast cancer arranged for MRM from 1/1/2019 to 9/2/2020.

Ethical approval for this research (Ethical committee N: 201819012.3, IRB: 0000402) was provided by ethical committee of NCI, Cairo University (CU), institutional review board (IRB).

Exclusion criteria include refusal to regional anesthesia, infection at the site of the procedure, local site anatomical abnormality, history of allergic reaction to research drugs, cases with pre-existing neurological deficits, and psychiatric illness, renal or liver diseases and failure to achieve adequate block within 30 min of administration after assessing using sensory assessment.

Cases were divided into two equal comparable groups: group I received US modified PECNB with BVC and group II received US- modified PECNB with BVC plus KET.

Pre-operative

The cases were instructed to use the Visual Analog Scale (VAS), a numeric rating scale from 0 (no pain) to 10 (the worst pain conceivable), to express their own pain levels prior to surgery.

Each patient was given 10 milligrams of valium and 150 milligrams of ranitidine orally the night before, and then maintained on a strict nil-by-mouth diet.

In the preparation area, blood pressure (BP), HR, were monitored and recorded.

Intra-operative

Theparticipants were subjected to a battery of tests, including an electrocardiogram (ECG), a non-invasive blood pressure reading, an arterial oxygen saturation reading, and an end-tidal carbon dioxide reading. In the operating theater, a multiparameter monitor was used to capture the patient's electrocardiogram (ECG), heart rate (HR), non-invasive blood pressure (NIBP), and peripheral oxygen saturation (SpO2).

GA was induced with IV midazolam 3ug/kg followed by propofol 1.5–2mg and fentanyl 1µg/kg. Anesthesia was sustained with isoflurane (minimal alveolar concentration 1-1.3) through a circular system, and tracheal intubation was assisted with 0.5mg kg of atracurium intravenous (IV) until loss of obey to verbal command.

Modified pectoral nerve block

After induction of anesthesia and before surgery, the modified PECNB was performed high-frequency linear array US instrument (Fujifilm sonosite M. Turbo US system) scans the area between the lateral third of the clavicle bone and the mid-axillary line. The cases were classified into two groups: Group A: the US probe was identified above the second, third rib into the fascial space between pectoralis major and pectoralis minor and inject 10 mL of BVC 0.25% after negative aspiration then third and fourth ribs between pectoralis minor and serratus and inject 20 mL of BVC 0.25% after negative aspiration and Group B: The US probe was identified above the second, third rib into the fascial space between pectoralis major and pectoralis minor and inject 10 mL of BVC 0.25% after negative aspiration then third and fourth ribs into the fascial space between pectoralis minor and serratus anterior muscles where 20 mL of BVC 0.25% plus KET hydrochloride (1mg/kg) were injected after negative aspiration.

Intraoperative hemodynamics (BP and HR every 5 min in the first hour and then every 10 min in the second hour then every 15 min in the rest of operation). In the post anesthesia care unit (PACU) BP, HR were monitored and recorded until discharge to ward. 30 mg ketorolac IV every 8 hours was given to all cases in the first 24 hours after surgery.

Follow-up

Pain intensity was measured with VAS score at 0.5h, 6, 12, 18, 24h postoperatively. Cases with VAS >4 were given morphine at a dose of 0.01 mg/kg IV, time to 1st dose of morphine, total morphine dose, case satisfaction using 5-point Likert scale (1, strongly agree; 2, agree; 3, neither agree nor disagree; 4, disagree; 5, strongly disagree) **[14]** and PONV score. There was a verbal questionnaire used to quantify PONV [15]: no sickness (none), mild nausea (some but not all), moderate vomiting (one incident), and severe vomiting (more than one attack) (15). At 30 minutes postoperatively, we used the pin prick technique to evaluate sensory block in the distribution areas of the lateral pectoral, median pectoral, intercostal, thoracodorsal, and long thoracic nerves, excluding the surgery incision.

Sample size estimation

The outcome variable is VAS score assessment, and based on previous research by Othman et al. **[1]**.

The mean (SD) for group A: 1.18 (0.33) and for group B: 0.47 (0.8). A large effect size of approximately 0.47 is expected. A total sample size of 144 will be sufficient to detect an effect size of 0.47, a power of 80%, and a significance level of 5%. This sample was increased to a total of 166 participants (83 participants per group) to compensate for nonparametric test usage. Sample size was calculated using G*Power program (University of Düsseldorf, Düsseldorf) [13, 16].

Statistical Analysis

IBM SPSS version 23 was used for the statistical analysis. (SPSS Inc., Chicago, IL). Mean, standard deviation, median were used to describe numerical data, while number and proportion were used to describe qualitative data.The correlation between qualitative factors was analyzed using Chi-square (Fisher's precise) and the correlation between matched nominal data was analyzed using McNemar (Cochran's Q).Regarding quantitative variables: Testing for normality was done using Kolmogrov-Smirnov test and Shapiro-Wilk test. If normally distribute variables, 2 way repeated measure analysis of variance (ANOVA) was used to test for group and time effect. If not normally distributed variables, for group effect: Comparisons between the median of the two independent groups were tested using Mann Whitney U test and for time effect: Comparisons between the median of the different time periods within the same group were tested using Freidman test that was followed by pairwise comparison using Analysis of signed-rank data using the Wilcoxon test. Statistical significance was assumed when the p-value was less than or equivalent to 0.05. All analyses were performed using a two-tailed test.

Results:

Cases' characteristics (age, BMI and ASA physical status) and duration of surgery were insignificantly different between both groups (table.1)

No statistically significant difference was observed between both groups regarding intraoperative HR, MAP and SpO_2. (Figure 1)

VAS at rest was insignificantly different at 0.5, 6, 12, 18 and 24h postoperatively and at movement it was insignificantly different at 0.5 and 6h postoperatively between both groups and was significantly lower at 12, 18 and 24h in group II than group I (table 2). Time of 1st rescue analgesia was significantly delayed at group II versus I (P value <0.001). Total morphine requirements were significantly less in group II versus I (P value <0.001) (Table.3)

Incidence of PONV was 10 (12.05%) cases in group I and 2 (2.41%) cases in group II. PONV was significantly less in group II versus I (P value =0.002).

Chest pain, hallucination, delirium and arrhythmia didn't occur in any cases in both groups. Satisfaction was insignificantly different between both groups (P value =0.889) (table.4)

Table 1: Cases' characteristics and duration of surgery of the studied groups

		Group I (n=83)	Group II (n=83)	P value
Age (years)		42.73 ± 8.55	43.49 ± 8.65	0.570
BMI (kg/m^2)		31.13 ± 4.28	30.71 ± 4.35	0.532
ASA physical status	**ASA I**	30 (36.14%)	31 (37.35%)	0.872
	ASA II	53 (63.86%)	52 (62.65%)	
Duration of surgery (min)		150.76 ± 16.77	151.98 ± 17.89	0.652

Data are presented as mean ±SD or frequency (%), BMI: body mass index, ASA: American Society of Anesthesiology

Table 2: VAS score at rest and movement of the studied groups

	Group I (n=83)	Group II (n=83)	P value
VAS score at rest			
0.5h	2 (1-3)	2(1-3)	0.479
6h	2(1-3)	2(1-3)	0.645
12h	3(2-3)	3(2-3)	0.363
18h	3(2-4)	3(2-5)	0.184
24h	3(1.5-4)	3(1-4)	0.546
VAS score at movement			
0.5h	2 (1-3)	2(1-3)	0.807
6h	2(2-3)	2(1-3)	0.095
12h	3(2-6)	2(1.5-3)	<0.001*
18h	3(3-5)	3(2-4)	0.034*
24h	3(2-4)	3(1-4)	0.009*

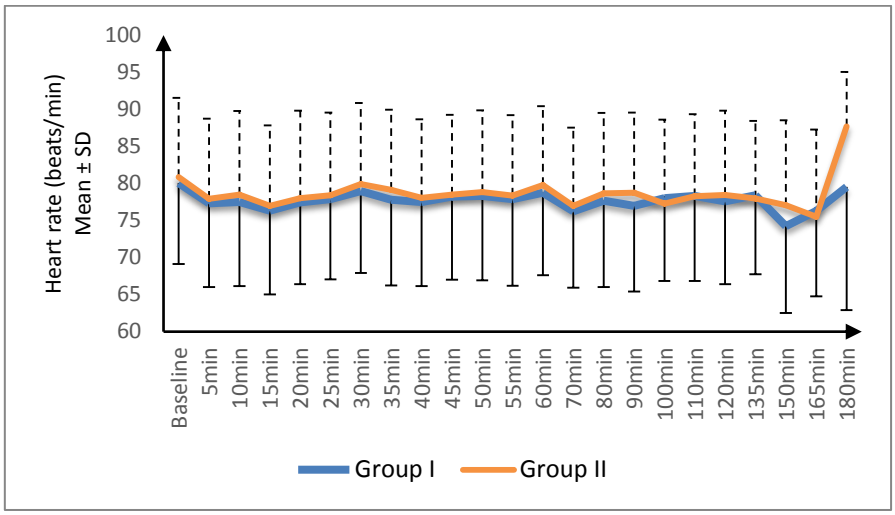
Data are presented as Median (IQR) VAS: visual analog scale, IQR: interquartile range

Table 3: Time of 1st rescue analgesia (h), Total morphine requirements (mg) of the studied groups

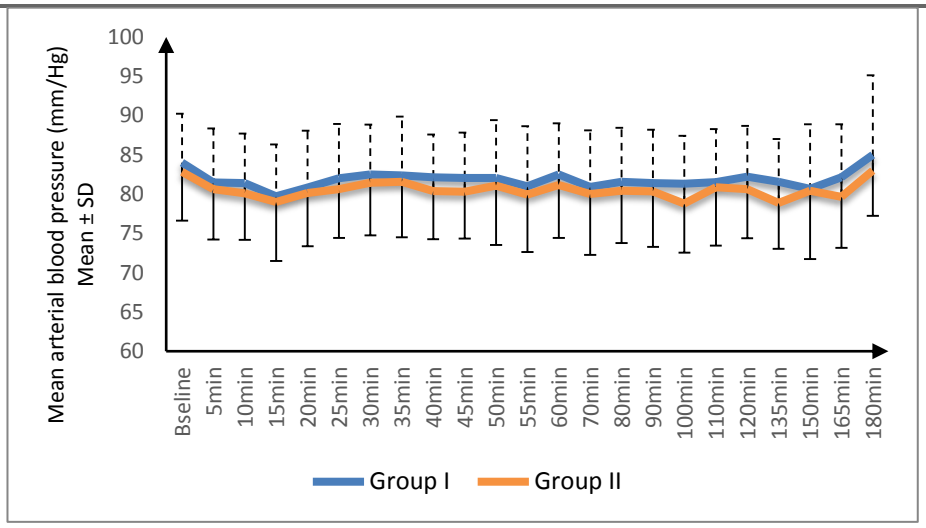
	Group I (n=83)	Group II (n=83)	P value
Time of 1st rescue analgesia (h)	15.33 ± 4.25	19.41 ± 3.36	**<0.001***

Total morphine requirements (mg)	9.9 ± 3.77	8.25 ± 1.81	**<0.001***

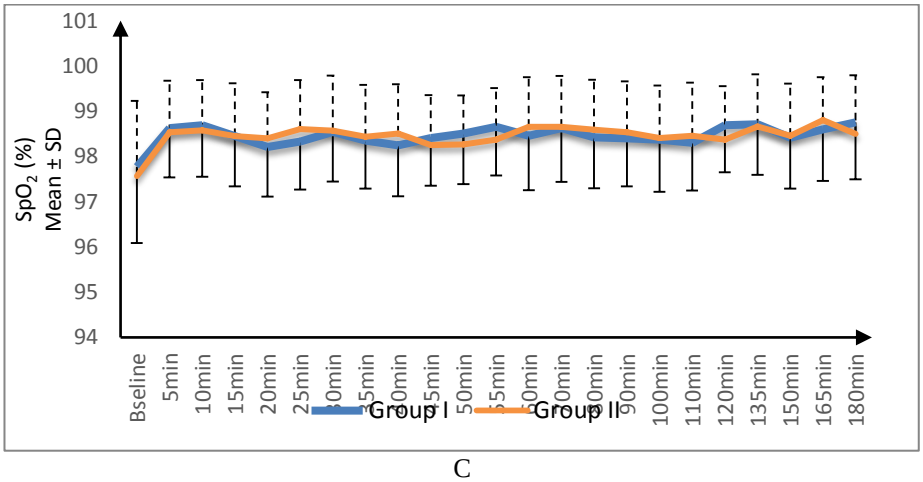
Data are presented as mean ±SD



A



B



C

Figure 1: Intraoperative (A)heart rate, (B)mean arterial pressure, (C) SpO2 of the studied groups

Table 4: Side effects and general satisfaction of parents of both groups

		Group I (n=83)	Group II (n=83)	P value
Side effects	**PONV**	10 (12.05%)	2 (2.41%)	**0.032***

	Chest pain	0 (0%)	0 (0%)	---
	Hallucination	0 (0%)	0 (0%)	---
	Delirium	0 (0%)	0 (0%)	---
	Arrhythmia	0 (0%)	0 (0%)	---
General satisfaction of parents	**Very satisfied**	40 (48.19%)	43 (51.81%)	0.889
	Satisfied	37 (44.58%)	35 (42.17%)	
	Neither satisfied nor dissatisfied	4 (4.82%)	3 (3.61%)	
	Dissatisfied	2 (2.41%)	1 (1.2%)	
	Very dissatisfied	0 (0%)	0 (0%)	

Data are presented as frequency (%)PONV: Postoperative nausea and vomiting, *: significant as P value ≤0.05

Discussion

In the present research, the intraoperative HR, MAP and SpO_2 were insignificantly different between both groups at all time measurements. In line with our results, Hefni et al [17] found that there were no statistically significant variations in perioperative hemodynamics, O_2 saturation, sedation scores, or side effects observed in the studied groups. Systolic and diastolic blood pressure, pulse rate, respiratory rate, and oxygen saturation were all found to be within normal ranges in the postoperative period, as was the case with our study (Othman et al., [1]), they were insignificantly different between the control and KET groups in both studies.

In the current work VAS was significantly less in group II versus I at 12h postoperatively (P value <0.001) and was insignificantly different at 0.5, 6, 18 and 24h postoperatively. In agreement with our results, Mohamed et al [18] reported that VAS was significantly less in KET (all over 24 h) versus controls (P value < 0.05). In agreement with our results, Lashgarinia et al [19] found that cases who received KET had less VAS scores than controls at all time intervals within the first twenty-four hours after surgery (all P 0.05). Also, following herniorrhaphy, Tverskoy et al. [20] injected 0.5 mg/kg KET locally to decrease pain and showed that it improved anesthesia quality and analgesia caused by 0.5% BVC.

In contrast, Othman et al. (2016) [1] found no statistically significant difference between KET and controls in the mean postoperative VAS score values at any time period or within the same group when comparing the values at each time period to the baseline (P > 0.05). However, at the 12-, 24-, and 48-hour marks, VAS values were reduced in the KET group versus controls, but this difference was insignificant.

Our research revealed that the time of 1st rescue analgesia was significantly delayed at group II versus I (P value <0.001). Also, total morphine requirements were significantly less in group II versus I (P value <0.001). In fact, a recent research supports our findings in which Hefni et al [17] revealed that postoperative morphine dose was significantly less in cases received BVC with addition of either KET versus cases received only BVC, (16.9±5.3 mg). Our results are confirmed by Kaur et al [21] who showed that the analgesia duration was significantly longer in KET group (27 mL of 0.5% ropivacaine + 2 mg/kg KET) (7.1 ± 0.89 h; P < 0.001) versus controls (27 mL of 0.5% ropivacaine) (6.76 ± 0.92 h; P < 0.001). Our results agree with those documented by Mohamed et al [18] who found that rescue analgesia was less in KET group (6.80 ± 3.19 mg) versus controls (13.33 ± 4.01 mg) (p < 0.05). In harmony with our findings, Lashgarinia et al [19] found that the KET group waited 8.93 ± 1.0 minutes longer for their first request for analgesics than the controls who waited for 7.30 ±1.9 minutes. Furthermore, 50 mg of KET combined with 2 mL of BVC 0.5% injected locally into the incision prior to anal operation by Kazemeini et al [22] was found to provide better postoperative analgesia than BVC 0.5% alone. In addition, Senel et al. (2014) [23] contrasted the analgesic effectiveness of 50 mg tramadol and 50 mg KET added to 40 mL 0.375% ropivacaine in axillary brachial plexus block and found that tramadol significantly prolonged the onset and duration and quality of the analgesia.

According to the current research, the incidence of PONV was 10 (12.05%) cases in group I and 2 (2.41%) cases in group II. PONV was significantly less in group II versus I (P value =0.002). Chest pain, hallucination, delirium and arrhythmia didn't occur in any cases in both groups. Similarly, Othman et al [1] reported that In the KET group, there were three cases of PONV and two cases of regurgitation, but no cardiac pain, arrhythmia, or psychological complications (hallucinations, delirium, dreams, nystagmus, and dissociative effects) were reported.

In disagreement with our findings, Kaur et al[21] observed sedation, nystagmus, and hallucinations in the KET group (27 mL of 0.5% ropivacaine + 2 mg/kg KET). This can be justified by the larger dose of KET they used than ours, as we add only 1 mg/kg of KET to the block.

Regarding the present research findings, satisfaction was insignificantly different between

both groups (P value =0.889). However, Hefni et al [17] reported that case satisfaction level was reported to be the higher in cases received KET as an additive than those who received BVC alone.

Limitations include that it was a single-center research, and the results may differ elsewhere, controls (no intervention or sham block) was not included due to ethical issues, it was a single blinded research, VAS was evaluated at rest only not during a cough or movement and follow up for 24 hours only.

Further clinical studies are needed with multicenter cooperation, blinding at multiple levels, and on larger scale to validate our findings, studies comparing these blocks to controls and investigating different doses of KET in order to pinpoint the optimal safe dosage that also significantly boosts analgesic effectiveness. It is possible to increase the efficacy of analgesics by employing multi-level injection or catheter placement methods. Serum levels of the drugs should be measured in the future studies; thus, we can see whether the effect of the research drugs is due to systemic absorption or some local mechanism.

Conclusions:

Administration of KET to US- modified PECNB with BVC increased the time until the first call for analgesia and decreased pain, total opioid consume, and PONV in cases undergoing MRM without causing significant adverse reactions.

Funding: No funding was obtained for this investigation.

Conflict of Interest: None of the authors has a conflict of interest.

Acknowledgements: Nothing to declare.

References:

1. Othman AH, El-Rahman AM, El Sherif F. Efficacy and Safety of Ketamine Added to Local Anesthetic in Modified Pectoral Block for Management of Postoperative Pain in Cases Undergoing Modified Radical Mastectomy. Pain Physician. 2016;19:485-94.

2. Gärtner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. Jama. 2009;302:1985-92.

3. Walder B, Schafer M, Henzi I, Tramèr MR. Efficacy and safety of case-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review. Acta Anaesthesiol Scand. 2001;45:795-804.

4. Kaya M, Oğuz G, Şenel G, Kadıoğulları N. Postoperative analgesia after modified radical mastectomy: the efficacy of interscalene brachial plexus block. Journal of anesthesia. 2013;27:862-7.

5. Sittl R, Irnich D, Lang PM. [Update on preemptive analgesia : options and limits of preoperative pain therapy]. Anaesthesist. 2013;62:789-96.

6. Bashandy GM, Abbas DN. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. Reg Anesth Pain Med. 2015;40:68-74.

7. Blanco R. Bloqueo pectoralnerve block. Manual de anestesia regional y econoanatomıa avanzada. 2011:92-5.

8. Blanco R, Diéguez García P, López Álvarez S, Pensado Castiñeiras A, Acea Nebril B. Eficacia analgésica del bloqueo de los nervios pectorales en cirugía de mama. Cir mayor ambul. 2011:89-93.

9. Haas DA, Harper DG. Ketamine: a review of its pharmacologic properties and use in ambulatory anesthesia. Anesthesia progress. 1992;39:61.

10. Burburan SM, Xisto DG, Rocco PR. Anaesthetic management in asthma. Minerva Anestesiol. 2007;73:357-65.

11. Klepstad P, Maurset A, Moberg ER, Oye I. Evidence of a role for NMDA receptors in pain perception. Eur J Pharmacol. 1990;187:513-8.

12. Colvin LA, Fallon MT. Opioid-induced hyperalgesia: a clinical challenge. Br J Anaesth. 2010;104:125-7.

13. Kiefer RT, Rohr P, Ploppa A, Dieterich HJ, Grothusen J, Koffler S, et al. Efficacy of Ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II research. Pain Med. 2008;9:1173-201.

14. Becker V, Heeschen V, Schuh K, Schieb H, Ziemssen T. Case satisfaction and healthcare services in specialized multiple sclerosis centres in Germany. Ther Adv Neurol Disord. 2018;11:17-9.

15. Nie Z, Cui X, Zhang R, Li Z, Lu B, Li S, et al. Effectiveness of Case-Controlled Intravenous Analgesia (PCIA) with Sufentanil Background Infusion for Post-Cesarean Analgesia: A Randomized Controlled Trial. J Pain Res. 2022;15:1355-64.

16. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39:175-91.

17. Hefni AF, Eldeek AM, Ismael SA, Shaban AR. Comparing Effect of Adding KET Versus Dexmedetomidine to BVC in Pecs- I I Block on Postoperative Pain Control in Cases Undergoing MRM. Clin J Pain. 2022;38:568-74.

18. Mohamed SA, Sayed DM, El Sherif FA, Abd El-Rahman AM. Effect of local wound infiltration with Ketamine versus dexmedetomidine on postoperative pain and stress after abdominal hysterectomy, a randomized trial. Eur J Pain. 2018;22:951-60.

19. Lashgarinia M, Naghibi K, Honarmand A, Safavi M, Khazaei M. Effect of Ketamine as an adjuvant in ultrasound- supraclavicular brachial plexus block: A double-blind randomized clinical trial research. Adv Biomed Res. 2014;3:232.

20. Tverskoy M, Oren M, Vaskovich M, Dashkovsky I, Kissin I. Ketamine enhances local anesthetic and analgesic effects of BVC by peripheral mechanism: a research in postoperative cases. Neurosci Lett. 2006;215:5-8.
21. Kaur S, Dhawan J, Gupta R, Chawla S. Comparison of Magnesium Sulfate and Ketamine with Ropivacaine in Supraclavicular Brachial Plexus Block: A Randomized Controlled Trial. Anesth Essays Res. 2020;14:143-8.
22. Kazemeini A, Rahimi M, Fazeli MS, Mirjafari SA, Ghaderi H, Fani K, et al. The effect of local injections of Bupivacaine plus Ketamine, Bupivacaine alone, and placebo on reducing postoperative anal fistula pain: a randomized clinical trial. ScientificWorldJournal. 2014;2014:424152.
23. Senel AC, Ukinc O, Timurkaynak A. Does the addition of tramadol and Ketamine to ropivacaine prolong the axillary brachial plexus block? Biomed Res Int. 2014;2014:686287.