

Research Article

Opioid-Free Anesthesia and Analgesic Quality During the Postoperative Period of Oncological Breast Surgery

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Abstract

Background: Pain is one of the most common symptoms in cancer patients. We can understand it as a multifactorial phenomenon. Breast cancer surgical treatment generates real damage to the structures and activates nociception which can generate persistent pain. Current anesthetic management is based on the use of opioids, which generate a large number of complications that can severely affect this group of patients, increasing morbidity and mortality. Opioid-free techniques have been shown to reduce complications and generate optimal anesthetic-analgesic management as well as decrease postoperative misuse. The purpose of this research is to compare both approaches and evaluate their impact on this population group. **Methods:** Simple, prospective, randomized, controlled blind clinical trial in 30 patients undergoing oncological mammary quadrantectomy a. The patients were divided into two groups study, the first (group A) received balanced general anesthesia with opioids as an analgesic strategy, the other group (group B) received general anesthesia balanced opioid-free supplemented with a PECs II regional block and/or Serratus (BRILMA) according to the patient's sonoanatomy, and ketamine-lidocaine as adjuvant drugs. Analgesia was assessed using the numerical pain scale at 2, 4, and 6 o'clock. The severity and impact of pain on the daily performance of patients were measured using the Brief Pain Inventory (BPI) short form in combination with clinical examination, the presence of postoperative complications, the length of stay in hours and the need for rescue with opioids. **Results:** 35% of the patients in group A required analgesic rescue with Tramadol to improve pain postoperative, while in group B only 10% needed it. 33% of the patients in group A completed their postoperative period with nausea and vomiting, while in the opioid-free group the percentage was only 1%. Referring to the length of hospital stay from surgery to discharge, group A was hospitalized for a period of 25 hours (SD=21.2), while group B was there for 15.2 hours (SD=8.7). **Conclusions:** Use of opioid-free anesthesia along with adjuvant strategies (drugs and nerve blocks) represent a safe and effective anesthetic strategy related with a lower incidence of complications from the use of opioids in the postoperative period, a lower consumption of analgesic rescues, a decrease in the length of hospitalization and a greater degree of comfort for the patient. This protocol represents an alternative when it comes to providing good intra and postoperative conditions for such a susceptible group of patients.

Keywords

Opioid Free Anesthesia, Cancer, Pain, Opioid Crisis Prevention, Opioid Misuse, Perioperative Pain Management, ERAS

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1. Introduction

The concept “Pain” is the sum of many factors assembled into an indivisible whole that cause suffering to the patient and his family, evident as physical, psychological, social and existential conditions [1]. In practice medically we can distinguish two algogenic components, pain nociceptive: originates with the activation of nociceptors due to tissue damage (which may be somatic or visceral), and the Neuropathic pain: occurs due to damage to the Nervous System Central (SNC) or Peripheral (SNP). Intensity is one of the most relevant dimensions and can be measured using different scales in a valid and unidimensional manner, while jointly evaluating other factors gives the analysis a multidimensional evaluation perspective [2]. Breast cancer is a common pathology in our medium, with surgical conduct for treatment. The pain acute postoperative period after breast surgery should be both direct damage to peripheral nerve fibers and to changes in neuro-endocrine profiles [3]. Lack of timely treatment can lead to Persistent Postmastectomy Neuropathic Pain, which can have a great impact on the patient's quality of life [4-6]. Opioids represent the best known option for pain management of these patients during the anesthetic and post-surgical analgesic procedure [7]. It is considered that Opioids are the cornerstone of pain treatment moderate to severe, but its use has been described as inducing tolerance and hyperalgesia due to overregulation of nociceptive compensatory pathways, “short analgesia, long hyperalgesia.” Properties are also attributed to this group of drugs. immunosuppressive and pro-angiogenic, which increases metastatic potential [8] and cancer recurrence rates in patients who have undergone oncological surgery for curative purposes [9]. Adverse effects of opioids, such as respiratory depression [10], postoperative sedation, ileus, urinary retention [11], nausea and vomiting are well known. Neurotoxic effects (delirium, sedation, myoclonus and hallucinations) are adverse effects caused by direct action in the central nervous system. The adverse reactions of Opioids bring with them an increase in complications, perioperative morbidity, delay in hospital discharge and major readmission rates [12]. With the aim of improving analgesia through the use of locoregional techniques and drugs with synergistic effects or additives at the minimum doses required to avoid their effects secondary, multimodal anesthesia emerges as a technique opioid-sparing drug that achieves improved efficacy and safety of anesthetic-analgesic management of patients. Regional anesthesia provides better intraoperative pain management.

Original article ratory and improves postoperative analgesia, decreases central sensitization and the development of hyperalgesia induced by opioids, preserves the function of the immune system by suppression of surgical stress and decreases opioid use in these procedures. Peripheral nerve blocks under direct ultrasound vision they have become easy and safe. The group of Blanco et al. has described 3 blocks suitable for the breast: the pectoral block I (Pecs I), the mod-

ified pectoral (Pecs II) and blockade of the cutaneous branches of the intercostal nerves in the mid-axillary line (BRILMA [16-19]. Perioperative intravenous lidocaine (a short-acting amide-type local anesthetic agent) is potent as sodium channel blocker, and is effective in reducing the incidence and severity of persistent postoperative pain [3], it also has analgesic, anti-inflammatory and antihyperalgesics as onco-anesthetic, acting simultaneously on peripheral nociceptors and sensitization central. Ketamine, on the other hand, has analgesic effects and mood stabilization by action at the level of the NMDA receptor and decreased serotonin and norepinephrine reuptake. Reduces the incidence of chronic postsurgical pain, opioid consumption, nausea and vomiting postoperative periods, and acute tolerance/hyperalgesia induced by opioids [20, 21]. This study aims to compare the effects of a OFA protocol (opioid free anesthesia) versus a balanced general anesthesia protocol with opioids in terms of quality of postoperative recovery, perception of pain, impact on quality of life, length of stay hospital stay and adverse effects in patients undergoing oncological breast quadrantectomy.

2. Materials and Methods

The guidelines of the Declaration of Helsinki were followed, Finland, from the World Medical Association (1964); reviewed and amended by the 64th General Assembly of Fortaleza, Brazil 2013. Prior authorization by the institution's ethics committee and having signed the relevant informed consent. A controlled clinical trial type study was carried out, longitudinal, prospective, comparative, randomized, simple blinding in 30 patients undergoing oncological breast surgery at the Allende Sanatorium in the city of Córdoba, New Headquarters Córdoba between the month of April and October 2022. Patients who underwent oncological breast quadrantectomy were included, aged between between 20 to 65 years old, with a BMI less than 30 and a classification ASA (American Society of Anesthesiologist) anesthetic risk equal to or less than II (two). Those patients who were allergic to any of the drugs employees, kidney failure, coronary artery disease, liver disease, and those patients who refuse to participate in the study. The patients were divided into 2 study groups. In both cases the patients received general anesthesia: the induction was performed under preoxygenation with 100% oxygen for 3 minutes. A loading dose of propofol was started at 2 mg/kg and rocuronium at 0.5 mg/kg, maintenance was performed with sevoflurane. at 0.5 MAC (minimum alveolar concentration). It was ventilated at patients by volume controlled ventilation mode at 6 ml/kg with a FiO₂ of 40%. In group A (control group) maintenance was carried out with remifentanyl at 0.25 mcg/kg/min, and the analgesic scheme prescribed during the intraoperative period was: dexamethasone 8 mg, ketorolac 60 mg and tramadol at a dose of 1

mg/kg. Associated to metoclopramide 10 mg for the control of nausea and vomiting postoperative. In group B, a block was performed after induction appropriate nerve for the area to be operated on (interpectoral ultrasound-guided (PEC2) and/or Serratus block (BRILMA Block) with 2 mg/kg bupivacaine 0.25%. For maintenance during surgery a ketamine load of 0.2 mg/kg was infused and then 5 mcg/kg/min as maintenance along with a load of lidocaine 1 mg/kg and 0.6 mg/kg/h as maintenance. As analgesic scheme received ketorolac 60 mg, metoclopramide 10 mg and dexamethasone 8 mg. Respirators were used to carry out this study. General Electric Care Station 650C, Pulse Oximeter, flow curve analyzer, Capnograph, Blood Pressure Monitor, Mindray Ultrasound Machine, 50 mm eco-refrangent needle, and the mentioned drugs previously. Analgesia was evaluated using the numerical pain scale, upon awakening, 2, 4 and 6 hours after the procedure, as well as the presence of nausea and vomiting, the need for rescues with opioids, and the length of hospital stay in hours. All this together with a brief pain scale (brief pain inventory BPI) in a questionnaire to be completed by interviewing the patient in the postoperative period together with its clinical evaluation. In the presence of pain of 4 or more on the Numerical Scale of pain, rescue was performed with 1 mg/kg of intravenous tramadol. Of Postoperative nausea and vomiting were treated patients with ondansetron 8 mg IV. Statistical methodology with the data collected from the records, a database was created of Excel type data, which was later used to statistical processing. For quantitative variables measures of centralization and dispersion were calculated (mean and standard deviation), and for the categorical variables, absolute and percentage distributions. Tests were applied Wilcoxon in the comparison of means and chi-square test in the correlation of categorical variables. In all cases A significance level equal to 0.05 was used. For statistical processing, the InfoStat statistical software was used. (V. 2020).

3. Results

The final sample of patients was made up of a total of $n = 30$ patients who underwent surgeries oncological breast oncology at the Sanatorio Allende de the city of Córdoba, Nueva Córdoba headquarters: 15 patients from Group A (anesthesia with opioids) and 15 who were administered opioids (Group B). The average age in the first group was 50.1 years ($SD = 7.9$) and in the second group the average age was 52.3 years ($SD = 9.5$), all ages were between 28 and 67 years maximum ($p = 0.203$). With the weight and height, BMI was calculated, indicating that in Group A, the majority had a normal BMI ($BMI \leq 24.9 \text{ kg/m}^2$) with 60%, while that, in Group B, this percentage was 53% (8 patients), the difference was not statistically significant ($p = 0.731$). It can be concluded that the groups were homogeneous with regarding the age and BMI of the patients (Figure 1).

Pain assessment

When evaluating pain with the Analogue Numerical Scale,

could observe that in both groups they had a decrease in pain values (Figure 2), however, the average values Group A (opioid anesthesia) at all times They were superior. When applying the test to compare the profiles, a statistically significant difference was demonstrated. Between Of the patients in the group that received opioid anesthesia, 35% needed analgesic rescue with tramadol to improve postoperative pain (Figure 3). While in the another group 10% needed it. The difference between percentages was not statistically significant.

Complications

Regarding complications, 33% of the first group presented nausea and vomiting (Figure 4), while in the group of women given opioids, this percentage was 7% (1 patient). In this case the difference in percentages was significant. The length of hospital stay since surgery in group A was 25 h ($SD = 21.2$), while for group B 15.2 h (Table 1). The difference between the means was statistically significant.

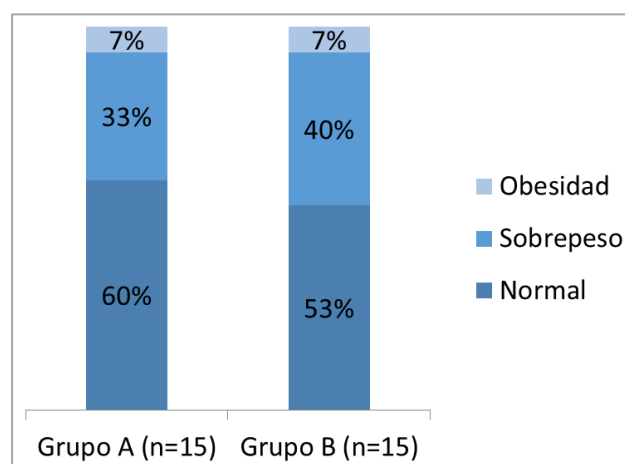


Figure 1. Distribution of BMI according to group ($p = 0.731$).

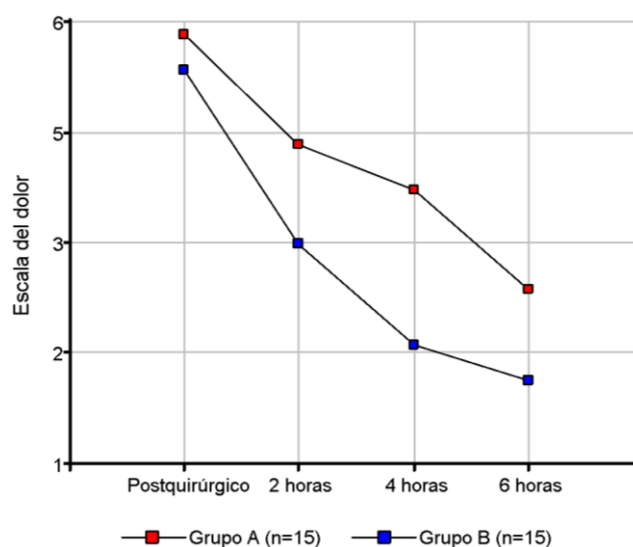


Figure 2. Graph of pain profiles according to group and moment of measurement.

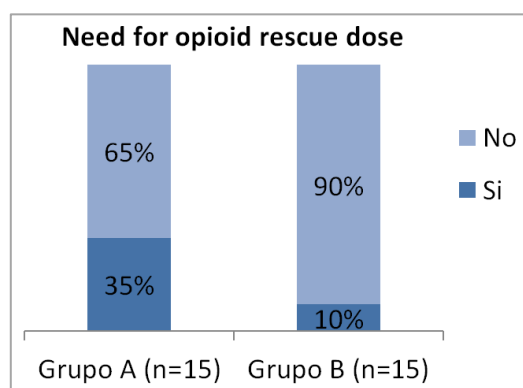


Figure 3. Need for rescue according to group ($p = 0.235$).

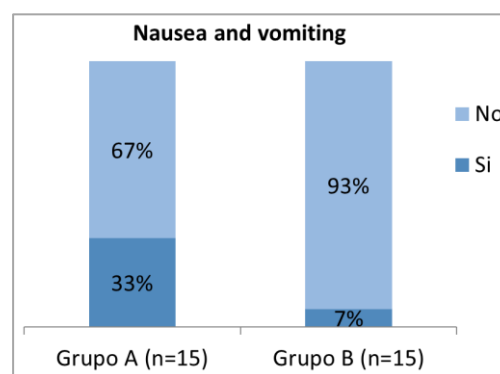


Figure 4. Presence of nausea and vomiting according to group ($p = 0.043$).

Table 1. Statistics of hospital stay time (hours) and degree of satisfaction at discharge according to group.

Variables	Group	Mean	D.E.	Min	Max	p-value
Length stay (horas)	Grupo A (n=15)	25,0	21,2	10	37	0,025
	Grupo B (n=15)	15,2	8,7	6	24	
satisfaction level at discharge	Grupo A (n=15)	7,0	1,3	5	9	0,047
	Grupo B (n=15)	8,2	1,1	6	10	

Finally, when evaluating the degree of comfort with pain in the At the time of discharge, it was observed that in both cases the average satisfaction was greater than 7 (Figure 5), however, the mean values of Group A were lower than those of the group at who were administered opioids. When applying the test, no significant difference between the means, possibly due to the number of cases.

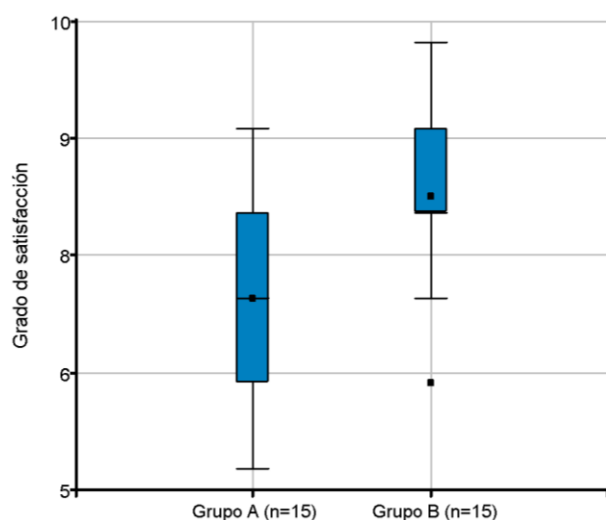


Figure 5. Box plots of the degree of comfort at discharge according to group.

4. Discussion

To carry out this intervention work, it has been divided the target population, those who had a diagnosis of breast cancer and were going to undergo a conservative oncological breast quadrantectomy, in two groups: a one of whom were provided with an anesthetic control plan, using balanced anesthesia with the use of opioids. To the another group was given opioid-free anesthesia. With the In order to assess perioperative analgesic management, the need of post-surgical analgesic rescues, the presence of complications, their degree of comfort, and the length of hospital stay. In a surgical procedure, real damage occurs to the structures of an organism, during this harmful stimulus physiological changes occur. The processing and encoding of this information is called nociception, which It should be a primary objective in every anesthetic-analgesic procedure. The transfer of thalamo-cortical sensory information is subject of modulation and inhibition, where several neurotransmitters used in these circuits have been found, such as gamma-aminobutyric acid (GABA), norepinephrine, 5-hydroxytryptamine (5-HT) and opioids, among others. The sensory transmission through the nerves in proximity to the tissue to be operated on, of the spinal cord, brain stem, thalamus, and cerebral cortex They are also susceptible to being modified and modulated. The use of opioids in anesthesia practice has been one of the great advances and

the most important in the management and the stability of the patient during the perioperative period. Although it has been demonstrated over time and in various studies that its use has been linked to multiple effects adverse events that increase morbidity and mortality and delay discharge hospital in patients undergoing surgery. driving away the health teams and patients of their related objectives to the protocols in outpatient surgery and rapid recovery protocols, for nausea, vomiting, ileus, respiratory depression, hyperalgesia, hormonal and immunological dysfunction, retention urinary, itching, among others. In addition to producing significant ventilatory complications [5], death due to respiratory depression and high postoperative opioid requirements. Remifentanyl, one of the most used opioids worldwide world for anesthetic maintenance, can play a role in acute opioid tolerance and opioid-induced hyperalgesia by a mechanism that is not yet understood Of course, this mechanism could raise some concerns on the role of opioid-induced hyperalgesia in the development of chronic pain in our patients. We can say that an opioid-free anesthesia, in which we can produce a disruption of these circuits by the use of different drugs in order to block the pain transmission [27], is by definition a type of “multimodal anesthesia”. Proposed term for anesthesia in which the effects of a combination of drugs affect to the circuits that process information and its transmission interrupts towards thalamo-cortical areas [14, 15]. It is also acquiring great importance in oncological surgery where there is growing concern about the immunosuppression produced by morphine and opioids, therefore which, it is believed that an opioid-free multimodal anesthesia could reduce the impact of the anesthetic-surgical procedure on the immune response and the possible recurrence of metastasis [6, 13, 18, 24]. Another no minor issue is the tolerance generated by its use. and the serious problem related to the abuse that occurs and happens in certain countries worldwide in the call “epidemic due to the use of opioids”, in which its excessive and uncontrolled use has led to the development of a worrying situation and generates enormous costs in policy and health plans. intervention in public health, in prevention and treatment of addictions and recovery from their harmful effects at the level social. Continuous stimulation caused by acute preoperative and perioperative pain has been correlated with the development of chronic pain in randomized controlled trials, for this reason For this reason, aggressive pain management in the perioperative period is of utmost importance. To avoid this, it has been decided by performing combined techniques, decreasing or supplanting the use of opioids with other drugs, thus avoiding their use. This has raised questions about how to obtain optimal intraoperative pain control, one of the pillars of general anesthesia, without using opioids [25]. As a result, the American Pain Society and the Society American Anesthesiologists recommends multimodal anesthesia for pain control to minimize opioid use. Current interventions include local anesthesia prolonged treatment and regional blocks for pain control. In this framework, regional anesthesia seems to be the

ideal technique in breast surgery; In fact, regional anesthesia could provide deep and selective analgesia to surgery, avoiding the systemic side effects of opioids; besides, interfascial blocks such as the PECS block technique They also allow you to avoid possible risks related to neuraxial and paravertebral techniques. The BPI was developed specifically for use in cancer patients and has been validated in patients with bone metastases, breast cancer, and postoperative patients with cancer. The BPI has been used in more than 25 studies in women with breast cancer. The construct validity found three factors, pain intensity, activity interference and affective interference that were invariant across age, disease and ethnicity. The brief pain questionnaire is a self-administered and easy-to-understand questionnaire. With the intention of reducing complications in select groups of patients, perioperative infusions of different drugs, adjuvants for general anesthesia; such as lidocaine, esmolol, dexmedetomidine, ketamine, sulfate magnesium, among others [7, 8, 22]. Thus reporting a significant decrease in the appearance of complications, where, generally using lower doses than those used by each individual drug is that we can associate them in a way ideal and profitably use their synergistic action, enhancing their therapeutic action and reducing adverse reactions [15, 16]. Patient characteristics, surgical intervention, and postoperative outcomes were compared between pre-ERAS® and post-ERAS® groups and between patient subgroups. outpatient and inpatient. Same-day discharge occurred in 58.6% of post-ERAS® patients versus 7.2% of pre-ERAS® patients ($p < 0.001$). ERAS® principles can be applied to patients with breast cancer and allow outpatient mastectomies without increased postoperative morbidity. Studies performed anesthesia in the ERAS protocol (Enhanced Recovery After Surgery) in different types of surgery with the aim of a postoperative period free of nausea and vomiting, without respiratory depression, ileus or urinary retention that delay discharge in these patients. This in favor of a better evolution postoperative period and discharge home in the shortest possible time. Regional pectoral nerve block (PECS) offers advantages over regional blocks such as paravertebral block and thoracic epidural block. One of the advantages is its greater safety and simplicity of the procedure, there is no sympathetic block as in paravertebral block or in epidural block, no need to use opioids, decreases pulmonary complications, decreases nausea as well as less time in the postoperative care unit. Recent studies reported better Blocking characteristics with PECS compared to PVB (Paravertebral Block). We choose a blocking technique insertion nerve at a single point, which provided good blocking results among the many variations available for Anterior chest wall nerve blocks. The blocking of pectorals reduced postoperative tramadol consumption in first 24 h and pain scores in the first 12 h. For all this we can position anesthesia free of opioids as one of the best alternatives in select groups of patients, especially in cancer patients, to reduce morbidity and mortality related to side effects of these drugs, hospital stay, improve

recovery, reduce the risks of tolerance, hyperalgesia, overuse and abuse. Previous studies on anesthesia for cancer surgery breast cancer aimed to identify the best block nerve (route, dose, site, technique, etc.), which could decrease the perioperative opioid requirement and provide a better analgesia. Previous studies have reported that regional analgesic techniques not only improve postoperative analgesia but also improve the quality of recovery after surgery. Two of the biggest advantages of OFA are the reduction of hyperalgesia and PONV. For the first, patients of OFA experienced significantly reduced pain scores in postsurgical pain, which could indicate a role in reducing opioid consumption. In addition to the decrease in the use of opioids and antiemetics in the Postanesthesia Recovery Unit in anesthesia regimens that save opioids, both important factors in discharge early. Therefore, we conclude that a technique free of well-made opioids like the one we have described offers a clinical benefit to this group of patients. At the moment, OFA techniques are gaining acceptance around the world, especially in areas of bariatric surgery and oncosurgery. Two of the greatest advantages of opioid-free anesthesia (OFA) found in our study are the reduction of hyperalgesia and the reduction of postoperative nausea and vomiting (PONV) [23]. Also, an increase was found in the perception of well-being, and decreased need for analgesic rescues along with decreased length of stay hospital [12, 13]. As Morioka H [16] expresses it, the use of pectoral nerve blocks significantly reduced the use of opioids such as remifentanyl intraoperatively and postoperative pain, although the requirement for analgesic rescues and PONV had no differences, possibly due to the intraoperative use of remifentanyl in the group that received regional block. Following the guidelines of Blanco et al. [18], we opted for the performance of the PEC II block, which is described as a modification of the PEC I with the ability to block the sensory transmission of the pectoral, intercostobrachial, intercostal nerves II, IV, V, VI and long thoracic nerve, describing a complete analgesia for breast surgery and widely recommending its use. On the other hand, Yusheng et al. [19] demonstrated that performing BRILMA blockade with ropivacaine for the management breast surgery anesthetic, was associated with better quality of recovery, better postoperative analgesia and greater satisfaction; Although we use bupivacaine in our work, its use It is also approved and recommended given its long action time, a beneficial profile that it shares with ropivacaine. Peltoniemi et al. [20], in their review of clinical pharmacokinetics of perioperative ketamine at low doses, demonstrated the ability to reduce opioid consumption and pain chronic postsurgical after surgical procedures specific. However, the effects have not been demonstrated long-term analgesics of ketamine in patients with pain chronic. In addition to analgesic properties, ketamine has fast-acting antidepressant effects, and may be useful in this population group, where depression It may be a present comorbidity, and may be related with the best scales of well-being and post-surgical comfort. Frauenknecht et al. [22],

in their review work, recall strong evidence that anesthesia that includes opioids does not reduces postoperative pain, but is associated with more nausea and postoperative vomiting [13, 14], compared to anesthesia without opioids, is that we also suggest avoiding its use, we design and implement an anesthesiaanalgesia protocol for breast surgery using free of charge techniques. opioids. Postoperative narcotic prescription was successfully eliminated without sacrificing pain control or increasing postoperative complications. The OFA protocol in surgery of breast cancer associated with regional anesthesia [24, 25] associated with a shorter hospital stay in hours and a lower complication rate [5]. Breast cancer surgeries with OFA protocols showed better analgesia scales [27], a shorter time for ambulation and a greater comfort have been associated with increased emotional adjustment and decreased psychological distress of patients. It is a recognized fact that poor intraoperative pain management has the capacity to generate persistent pain. breast postoperative [26, 27]. Being a defined entity due to persistent pain for more than three months after the surgical procedure and not having followed up these patients for a prolonged time beyond the immediate postoperative period is that we cannot infer the impact of our intervention on this variable. Being subject to a future extension of this work, the answer to this question. The protocol we present offers a safe alternative for whom regimens containing opioids. This study provides a preliminary indication of that certain balanced general anesthesia regimens free of Opioids are more effective with respect to analgesic quality than the current standard with the use of balanced anesthesia general with opioid use, generating fewer incidences of complications. with the aim of reducing prescriptions of opioids, improve patient recovery and reduce the utilization and overall costs of care resources medical.

5. Conclusions

The use of an "Opioid-Free Anesthesia", making use adjuvant to nerve block appropriate for the site to be operated is related to a lower incidence of complications due to use of opioids in the postoperative period, while at the same time associated with a decrease in hospital stay time and a greater degree of comfort, also showing itself as a reliable procedure, and making less use of rescue doses of post-surgical opioids. The use of opioids anesthetics during surgical procedure and as analgesics for aftercare is considered the cornerstone of treatment for moderate to severe pain, but it has been described that its use induces tolerance and hyperalgesia due to upregulation of nociceptive compensatory pathways, "short analgesia, long hyperalgesia". The adverse reactions of opioids bring with them an increase in complications, perioperative morbidity, delay in hospital discharge, older readmission rates and misuse. For the Hispanic/Latino population, opioid misuse stemming from overuse of pain relievers is also a major pathway to opioid misuse many times started from the perioperative period. Use of opioid-free anesthesia along

with adjuvant strategies (drugs and nerve blocks) represent a safe and effective anesthetic strategy related with a lower incidence of complications from the use of opioids in the postoperative period, a lower consumption of analgesic rescues, a decrease in the length of hospitalization and a greater degree of comfort for the patient. This protocol represents an alternative when it comes to providing good intra and postoperative conditions for such a susceptible group of patients.

Abbreviations

BMI	Body Mass Index
NMDA	N-Methyl-D-aspartate
MAC	Minimum Alveolar Concentration
SD	Standard Deviation
PVB	(Paravertebral Block).
PEC	Pectoral Nerve Block
GABA	Gamma-aminobutyric Acid
5-HT	5-hydroxytryptamine
BPI	Brief Pain Inventory
BRILMA	Block of the Lateral Branches of the Intercostal Nerves in the Middle Axillary Line
PONV	Postoperative Nausea and Vomiting
OFA	Opioid Free Anesthesia
ERAS	Enhanced Recovery After Surgery

Author Contributions

Rodrigo Sebastian Parada Heit is the sole author. The author read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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