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Research Article

A Comparative Analysis of Opioid-Based Anesthesia (OBA) and Opioid-Free Anesthesia (OFA) in Modified Radical Mastectomy: Effect on Hemodynamics Changes Intraoperative, Inflammatory Cytokine (IL-6) Levels, Pain Degree, and Postoperative Opioid Requirements

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ABSTRACT

Background: Acute postoperative pain following modified radical mastectomy (MRM) remains a significant clinical problem, affecting patients' quality of life. Opioid-based anesthesia (OBA), while effective for analgesia, is associated with adverse effects, including increased interleukin-6 (IL-6) levels, and the higher the IL-6 levels, the higher the likelihood of breast cancer recurrence. Opioid-free anesthesia (OFA) has emerged as a potential alternative to mitigate these effects. This study aimed to compare the impact of OBA and OFA on intraoperative hemodynamic stability, IL-6 levels, postoperative pain degree, and total postoperative opioid requirements.

Methods: This was a single-blind randomized clinical trial involving 30 patients undergoing MRM, allocated into two groups: Group I received OBA, and Group II received OFA. Parameters assessed included intraoperative hemodynamic changes, serum IL-6 levels, postoperative pain degree, and total postoperative opioid requirements.

Results: The OFA group had significantly lower IL-6 levels at 24 hours post-surgery. The OFA group also demonstrated more stable intraoperative hemodynamics, significantly lower postoperative pain degree, and reduced postoperative opioid (fentanyl) requirements compared to the OBA group.

Conclusion: OFA is better than OBA in modified radical mastectomy surgery. OFA significantly reduced IL-6 levels as a marker of inflammation, resulted in lower recurrence of breast cancer, reduced the degree of postoperative pain, maintained hemodynamic stability during the procedure, and reduced postoperative opioid requirements. These findings suggest that OFA is a more effective and safe anesthetic option in controlling pain and surgical stress response.

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Introduction

Modified radical mastectomy is one of the main surgical procedures performed on patients with breast cancer [1]. The side effect of modified radical mastectomy is pain. The incidence of pain reaches 53% six months after mastectomy [2]. Chronic pain is most common in patients after modified radical mastectomy [3]. Post-mastectomy pain can be persistent with an incidence of 20-68% [1]. Post-mastectomy pain has a significant impact on mental health, emotional well-being, and social relationships [4]. The persistent pain causes a 44.98% decrease in quality of life in post-mastectomy patients [5].

Factors that influence the likelihood of developing postoperative pain into a chronic condition include additional treatment, age, gender, psychosocial status, preoperative pain, type of surgery, analgesic treatment, and genetic factors [1]. Effective postoperative pain control is an important component of preventing acute pain from developing into intractable chronic pain [2]. Therefore, appropriate pain management strategies are critical in improving postoperative outcomes and accelerating the patient's overall recovery and rehabilitation process.

Pain arises in response to tissue stimulation during surgery, even when the patient is under anesthesia. These stimuli can trigger activation of the autonomic nervous system, characterized by increased heart rate and blood pressure, as well as the release of stress biomarkers such as cortisol and catecholamines [6]. Therefore, controlling the autonomic response to surgical stimuli is one of the main requirements of anesthesia. In this regard, opioids are the drugs of choice to achieve intraoperative hemodynamic stability [6]. However, the use of opioids has various side effects, such as nausea, vomiting, itching, constipation, respiratory depression, and urinary retention. In addition, intraoperative consumption of high doses of opioids leads to an increased risk of opioid-induced hyperalgesia and postoperative nausea and is associated with longer recovery time [7].

The limitations of opioids in perioperative pain management have prompted a consensus from the American Society of Breast Surgeons to reduce the use of opioids in patients undergoing breast surgery [7]. Perioperative opioid use needs to be minimized or even eliminated to reduce the risk of adverse effects [6]. An anesthetic approach without opioids is also emerging as a recommended strategy, as it is proven to provide adequate pain relief, maintain hemodynamic stability during surgery, and reduce the need for additional analgesics and the incidence of postoperative nausea and vomiting [8].

Interleukin-6 (IL-6) is a proinflammatory cytokine that plays a role in inflammatory responses due to malignancy, trauma and surgery and may mediate pain through increased C fibers and cancer-related neuropathic pain [9-10]. IL-6 levels are also a prognostic factor in several cancers, including breast cancer [11]. Studies have shown that IL-6 levels increase significantly after mastectomy and are positively associated with the use of opioid-based anesthesia [12-13]. In contrast, opioid-free anesthesia is reported to reduce IL-6 levels, pain scores, and postoperative analgesic requirements [14-15]. Therefore, this study aimed to compare opioid-free anesthesia with opioid-based anesthesia on hemodynamic changes during surgery, IL-6 levels, pain scores, and postoperative opioid requirements in patients undergoing modified radical mastectomy.

Methods

This study was an experimental study with a single-blind randomized clinical trial design conducted at Dr. Wahidin Sudirohusodo Hospital Makassar and a teaching network hospital. The study began after obtaining permission and lasted until the minimum number of samples was met. The study population was patients who would undergo modified radical mastectomy surgery. A total of 30 subjects who met the inclusion criteria were selected by consecutive sampling and randomly divided into two groups of 15 patients each, namely group I receiving OBA and group II receiving OFA.

Inclusion criteria in this study included patients aged 19-65 years, having a body mass index (BMI) between 18.5 - 29.9 kg/m^2, and having ASA II physical status. Exclusion criteria included patients with a history of hypertension, diabetes mellitus, heart disease, acute/chronic infection, neurological or cognitive impairment, or allergy to the drugs used, as well as patients taking immunosuppressants or being pregnant. Patients who underwent conversion to general anesthesia with an endotracheal tube or withdrew from the study were categorized as dropouts.

Patients in the OBA group received fentanyl and propofol during anesthesia, while the OFA group received a combination of dexmedetomidine, lidocaine, and propofol without intraoperative opioid administration. Parameters observed included hemodynamic response during surgery, postoperative pain scale using Numeric Rating Scale (NRS), postoperative opioid requirement within 24 hours, and IL-6 levels measured preoperatively (T0), 6 hours (T1), and 24 hours postoperatively (T2). Data were analyzed using the Shapiro-Wilk test for normality, as well as the unpaired t-test or Mann-Whitney according to data distribution. The significance level was set at 5%, or 0.05. Data were analyzed using SPSS 27 with the Mann-Whitney test and independent t-test. The study was conducted after obtaining a research permit from the Hasanuddin University Makassar Ethics Committee number 1099/UN4.6.4.5.31/PP36/2024.

Results

This study involved 30 female patients undergoing modified mastectomy radical surgery, who were randomly divided into two groups based on the anesthesia procedure: group I given OBA group II given OFA. Analysis of characteristics showed no statistically significant differences in terms of age, BMI, and ASA PS ($p>0.05$) (Table 1).

Comparison of IL-6 levels was used as a marker of systemic inflammation in both intervention groups. IL-6 levels were measured at three time points, namely before surgery (T0), 6 hours postoperatively (T1), and 24 hours postoperatively (T2).

Comparison of the difference in IL-6 levels between measurement times in each group to assess the magnitude of the postoperative inflammatory response that occurs due to differences in anesthetic approaches. The results of the comparison of the difference in IL-6 in the two groups can be seen in (Table 2). Analysis From (Table 2), it can be seen that there is a significant difference in the difference in IL-6 changes in the two groups 24 hours postoperative. It is shown that the OFA group has a smaller change in IL-6 levels compared to the OBA group indicating the OFA group has a lower chance of recurrence than OBA.

Comparison of pain degree based on the Numeric Rating Scale (NRS) measured at four time points, namely before surgery (T0), 2 hours postoperatively (T1), 6 hours postoperatively (T2), and 24 hours postoperatively (T3). The results of the comparison of pain degree between groups can be seen in (Table 3).

From (Table 3), it can be seen that there is a significant difference in the degree of pain 2 hours, 6 hours, and 24 hours after surgery in group I and group II, (Table 3) also show a significant difference in the degree of pain at each time between the three groups; it was found that the lower degree of pain was in group II OFA than group I OBA, indicating that OFA provided better postoperative pain management. Evaluation of mean arterial pressure (MAP) was performed by comparing changes in values from baseline (MAP_0) at four time points after anesthesia induction, namely 5 minutes after induction (MAP_1), 15 minutes after induction (MAP_2), 30 minutes after induction (MAP_3), and 45 minutes after induction (MAP_4). This change was calculated as the difference between the MAP value at each measurement time and the baseline MAP value. The results of the comparison of the MAP difference between the two groups are presented in (Table 4).

From (Table 4), we can see a significant difference in MAP changes only 5 minutes after the start of anesthesia induction, but group II OFA showed more stable changes over time. Heart rate (HR) evaluation was performed by comparing changes in values from baseline (HR_0) at four time points after anesthesia induction, namely 5 minutes after induction (HR_1), 15 minutes after induction (HR_2), 30 minutes after induction (HR_3), and 45 minutes after induction (HR_4).

These changes were calculated as the difference between the HR value at each measurement time and the baseline HR value. The results of the comparison of HR differences between the two groups are presented in (Table 5).

The analysis results showed significant differences in HR changes between the two groups at all measurement times. Group I OBA experienced the highest HR increase consistently at all times, while group II OFA showed a much lower increase. Group II OFA tended to have the most minimal HR changes, indicating that OFA provided better hemodynamic stability.

A comparison of total postoperative opioid requirements (fentanyl) over 24 hours in the two intervention groups is presented in (Table 6).

From (Table 6), it can be seen the need for opioid fentanyl 24 hours postoperative in both groups. There is a significant difference in the need for opioids (fentanyl) in the two groups. Group II OFA has a lower need for opioids (fentanyl) compared to group I OBA, indicating that OFA provided better postoperative pain management.

Table 1- Characteristics of research sample

Characteristics	Group I	Group II	P value
Age (years)[1]	42.87± 9.03	44.20± 8.35	0.681^{ns}
BMI (kg/m2)[2]	22.80± 1.78	22.60± 1.55	0.678^{ns}
ASA PS (II)	15	15	-

*Numerical data (age, BMI) are presented as mean ± standard deviation (SD) and tested by[1]independent t test or a [2]mann-whitney u test, ns: not statistically significantly different. **Categorical data (ASA PS) are shown as frequency counts (n).

Table 2- Comparison of difference in IL-6 levels between groups

Group	Interleukin-6 (pg/dL)		Value of p[2]
	T0-T1	T0-T2	
I	23.88 ± 19.50	31.51± 20.38	0.419^{ns}
II	15.47± 10.77	14.15± 9.48	0.006^{*}

*Numerical data are shown with mean± standard deviation. Data were tested by [1]Mann-Whitney U test and. Values of $p<0.05$ were significant; *significant, ns: not statistically different.

Table 3- Comparison of postoperative NRS difference between groups

Group	NRS			P value
	T0-T1	T0-T2	T0-T3	
1	1.60± 1.18	1.53± 1.06	0.13 ± 0.64	0,002*
2	-0.07± 0.13	-0.13± 1.25	-0.93± 1.10	0,005*

*Numerical data are shown with mean± standard deviation. Data were tested by Mann-Whitney U test. Values of p<0.05 were significant; *significant, ns: not statistically different.

Table 4- Comparison of difference in MAP changes between groups

TAR Change	Group I	Group II	P value
ΔMAP_{0-1}	8.20± 4.00	4.13± 3.25	0.005*
ΔMAP_{0-2}	14.00± 4.72	13.87± 2.70	0.925ns
ΔMAP_{0-3}	15.47± 3.40	15.40± 2.41	0.951ns
ΔMAP_{0-4}	14.33± 3.22	15.40± 2.20	0.299ns

*Numerical data are shown with mean± standard deviation. Data were tested by independent t test. The value of p<0.05 is significant; *significant, ns: not statistically different.

Table 5- Comparison of HR Changes between Groups

HR Change	Group I	Group II	P value
ΔHR_{0-1} [2]	8.67± 5.25	2.67± 2.50	0,000*
ΔHR_{0-2} [2]	19.40± 7.46	5.07± 4.38	0,000*
ΔHR_{0-3} [2]	19.80± 7.66	5.67± 4.76	0,000*
ΔHR_{0-4} [1]	17.00± 7.26	6.27± 6.08	0,000*

*Data are shown with mean ± standard deviation (SD). Data were tested by [1]independent t test and [2]Mann-Whitney U test. p<0.05 was significant; *significant.

Table 6- Opioid Requirement

Group	Total fentanyl requirement in 24 hours (µg)	p
1	277.33 ± 36.93	0.000*
2	68.00± 21.11	

*Data are shown as mean ± standard deviation (SD). Data were tested by the Mann-Whitney U test. p<0.05 was significant; *significant.

Discussion

This study included 30 patients who underwent radical mastectomy procedures with two different anesthetic approaches, OBA and OFA. Analysis of the baseline patient characteristics showed that there were no significant differences between the two groups in all three parameters (Table 1). This indicates that the two groups were similar in terms of age, body mass index (BMI), and ASA status. This homogeneity is important to ensure that differences in postoperative outcomes are more likely to be due to the anesthetic technique used rather than confounding factors such as the patient's initial physical condition [16].

Surgery is known to trigger systemic stress and inflammatory responses characterized by increased levels of proinflammatory cytokines such as IL-6 which is also one of the biomarkers that could predict recurrence of breast cancer. In this study, IL-6 levels showed a significant increase over time in each group, indicating activation of the postoperative inflammatory response. However, from (Table 2), it can be seen that there is a significant difference in the difference in IL-6 changes in the two groups 24 hours postoperative. It is shown that the OFA group has a smaller change in IL-6 levels compared to the OBA group. This is in line with previous studies that opioids can increase the release of proinflammatory cytokines such as IL-6 through activation of the innate immune system, so the use of opioids in anesthesia is likely to amplify the postoperative inflammatory response. IL 6 can be used as a biomarker to predict breast cancer recurrence; with lower IL 6 levels 24 hours after surgery, the OFA technique results in a lower likelihood of recurrence [10-11,13].

Pain assessment using the Numeric Rating Scale (NRS) showed that patients in group II (OFA) experienced less pain than group I (OBA) at T1, T2, and T3 with significant differences, while at T0 there was no significant difference (Table 3). Group I (OBA) showed a high increase in pain early postoperatively (T1 and T2), while group II (OFA) showed a more stable pain trend and tended to decrease faster. This indicates that the OFA approach is more effective in reducing pain intensity from the early phase to 24 hours postoperatively. These results are in line with research by Khaled *et al*., who found that the use of OFA in elderly patients undergoing arthroscopic shoulder surgery resulted in lower pain scores in the first 24 hours postoperatively [17]. Evaluation of hemodynamic parameters in this study was

conducted through measurement of MAP and HR at four time points during the perioperative period. The results showed that changes in MAP were only significantly different at $\Delta MAP_{(T1-T0)}$, where the OBA group had a higher increase than the OFA group, while at other points there were no significant differences (Table 4). Meanwhile, changes in HR showed significant differences at all time points of observation, with the OBA group experiencing a significantly higher increase than the OFA (Table 5). This increase indicated greater sympathetic stimulation intraoperative pain as well as direct side effects of opioids on vascular tone and cardiac activity. In contrast, the OFA group showed better hemodynamic stability, indicating more effective pain control and lower autonomic nervous system activation. These results support the theory that the use of opioids in anesthesia may increase sympathetic nervous system activation and catecholamine release, thereby worsening hemodynamic stability [6].

In addition, the 24-hour postoperative fentanyl requirement in group I OBA was significantly higher than group II OFA with a P-value <0.05 (Table 6). These results suggest that patients receiving opioid-based anesthesia required more opioids to control postoperative pain. In contrast, the group using the opioid-free approach showed better analgesic efficiency, with significantly lower opioid requirements. This emphasizes the importance of a multimodal approach to non-opioid analgesia in reducing opioid consumption and avoiding its negative impact [18]. Overall, the OFA approach provides better results than OBA in terms of decreased IL-6 levels as an indicator of inflammation and recurrence prediction of breast cancer, more stable and effective surgical pain control, maintaining postoperative hemodynamic stability, and decreased need for additional opioids. These findings confirm the benefits of an opioid-free approach in major surgery, such as mastectomy, in terms of inflammation, recurrence prediction, and pain management. This study also has some limitations, such as the short duration of observation, which may limit the accuracy of predicting recurrence in breast cancer. In addition, the inflammatory biomarkers evaluated were limited to one type, interleukin-6, without including other biomarkers that are also relevant in inflammatory processes and surgical stress.

This may limit the understanding of the patient's immune response to the anesthetic technique used. Therefore, further studies with longer duration and wider use of biomarkers are needed to strengthen these findings.

Conclusion

OFA is better than OBA in modified radical mastectomy surgery. OFA significantly reduced IL-6 levels as a marker of inflammation, resulted in lower recurrence of breast cancer, reduced the degree of postoperative pain, maintained hemodynamic stability during the procedure, and reduced postoperative opioid requirements. These findings suggest that OFA is a more effective and safe anesthetic option in controlling pain and surgical stress response.

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