Comparative Effects of Remifentanil and Fentanyl on Inflammatory Stress Response in Mastectomy Surgery with General Anesthesia: A Case Series

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Abstract

Malignancy associated with chronic inflammation and stress response events by the surgical procedure. The use of an opioid such as remifentanil can decrease stress response that may be measured by leukocyte, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume, blood sugar, and C-reactive protein (CRP). This was a randomized, single-blind study, with a total sample of ten patients, and they were divided into two groups: 1. remifentanil group (0.1–0.3 mcg/kg body weight [BW]/min) and fentanyl group (intermittent 0.5–1 mcg/kg BW every 60 min). The patients’ blood were collected two times before and 24 h after surgery. Inflammation markers such as total leukocyte value, NLR, PLR, and CRP were increased in two groups. Even PLR postoperative remains high in both group, but in remifentanil group was lower than fentanyl group. There were no differences between the two groups, but remifentanil was found better to suppress the postoperative PLR rather than in the fentanyl group.

Keywords: C-reactive protein, fentanyl, mean platelet volume, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, remifentanil

INTRODUCTION

Surgery causes a change in systemic leukocytes. Measuring the total of leukocyte, neutrophils, lymphocytes, platelet, and C-reactive protein (CRP) as a stress response indicator. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are markers that can be assessed easily to indicate systemic inflammation.[1,2]

Remifentanil is an ultrashort-acting synthetic opioid that is more potent than fentanyl. The unique of remifentanil is expected to suppress the response of inflammatory stress due to surgical trauma by suppressing the nociceptive process modulation in the hypothalamus–pituitary–adrenal (HPA) axis.[3,4]

The present study aims to compare remifentanil to fentanyl in suppressing the leukocytes, NLR, PLR, MVP, blood sugar, and CRP after surgery as stress response on the mastectomy procedure.

CASE REPORT

The number of samples participating in this pilot study was ten participants. Participants are women aged 18–65 years old who will undergo a mastectomy surgery with the physical status of the American Society of Anesthesiologists 1 and 2. Participants were divided into two groups, namely the remifentanil (R) group and fentanyl group (F). The sample of this study was collected by prospective randomized. Patients were given informed consent in advance. In the preparation room, the participants were given the premedication of midazolam 0.05 mg/kg body weight, ketorolac 30 mg, and ketamine 0.1 mg/kg BW intravenously. In the R group, remifentanil administered at a dose of 1 mcg/kg BW in 60 s, propofol 2–3 mg/kg BW, atracurium 0.5 mg/kg BW, 5 min after performed intubation, the patient
were monitored with the maintenance during procedure with sevoflurane 2 volume% with remifentanil continuous at a dose of 0.1–0.3 mcg/kg BW/min. In the Group F, fentanyl administered at a dose of 2 mcg/Kg BW, propofol 2–3 mg/kg BW, atracurium 0.5 mg/kg BW, after 5 min performed intubation, the patients were monitored with the maintenance during the procedure with fentanyl intermittent 0.5–1 mcg/ KgBW every 60 min intravenous and sevoflurane 2% volume. Morphine is given for analgetics after surgery in the ward. The inflammatory stress response due to surgical procedure uses total leukocytes, neutrophil-to-lymphocytes ratio, PLRs, mean platelet volume (MPV), and random blood sugar. Blood samples were taken through peripheral blood with two different times, preoperative and 24-h postoperative.

**Results**

In both R and F groups, the inflammatory marker is a change in the number of leukocytes compared to the baseline preoperative value. Graph 1 presents the preoperative and postoperative comparison data in both groups.

The inflammatory stress response assessed from NLR and PLR increases in both groups. However, on PLR, remifentanil is better at suppressing the increase in postoperative PLR value. This increases due to stress response in the form of an increase in neutrophil count and decreased lymphocytes due to cytokines released by surgical trauma. Graphs 2 and 3 represent the comparisons of NLR and PLR values between the two groups when pre- and postoperative. The CRP value is associated with an acute-phase response as the impact of the production of interleukin-6 (IL). The CRP’s value in this study showed that the fentanyl group was better at suppressing the postoperative CRP compared to the remifentanil group [Graph 4]. As for MPV and blood sugar values [Graph 5 and Table 1] between the two groups do not indicate any difference.

**Discussion**

Malignancy is an abnormal growth of tumor cells, and many of the inflammatory mediators involved, for example, cytokines, chemokines, prostaglandins, and cyclooxygenase cause tumor growth by the suppression of the system immunity, increasing resistance to apoptosis, and promotion of angiogenesis. Anesthesia procedure in a cancer patient is associated with this inflammatory response.[1]

The surgical stress response can trigger systemic leukocyte changes after surgery, namely leukocytosis, neutrophilia, or lymphopenia. The neuroendocrine activated system during anesthesia and surgery results in the release of neuroendocrine and cytokine hormones. During anesthesia and surgery, there is a change in the immune system that affects the physiological response, which relates to the expansion of surgery, the patient’s age, general health conditions, medication, and blood transfusions.

In this study, both groups showed an increase in total leukocytes. There is nothing dominant in both groups in suppressing the total increase in leukocytes from baseline values. In a subclass of leukocytes, NLR and PLR are increased. This may be caused by a surgical stress response causing an increase in neutrophil production and an increase in apoptosis lymphocytes. NLR and PLR enhancements may be associated with poor outcome and complications in the carcinoma surgery.
NLR and PLR in peripheral blood are a simple marker for systemic inflammatory response. NLR is essential for the diagnosis in some pathological circumstances, characterized by systemic inflammatory responses, such as diabetes mellitus, coronary artery disease, ulcerative colitis, and inflammatory arthritis. Several subclasses of leukocytes show that an increase of neutrophils and a decrease of lymphocytes will increase the NLR associated with the acceleration of mortality and morbidity in carcinoma patients. The NLR increase from baseline values demonstrates a poor prognosis for survival in any type of carcinoma patients. NLR is not only a provider of patient’s data but also a patient’s prognosis.

Endogenous anti-inflammatory anticancer and precoagulation responses can be detected with PLR. PLR is also more sensitive as a prognostic factor for breast cancer cases. Some studies show an increase in NLR numbers, and PLR shows increased inflammatory and associated with organ damage, cardiovascular risk, and death in case of malignancy.

Cytokines play an important role in the inflammatory response due to trauma and surgery. Cytokines have localized effects in mediation and maintain an inflammatory response due to trauma, as well as initiating systemic changes occurring. After a major surgery, the main cytokines released include IL-1, tumor necrosis factor α (TNF-α), and IL-6. IL-1 and TNF-α are released from the activation of macrophages and monocytes in damaged tissues. This will further stimulate the production and release, especially IL-6, as the primary cytokine responsible for systemic changes known as the acute-phase response. The CRP value will increase with IL-6 parallelly.

PLR develops into a marker that provides information on shifting the number of platelets and lymphocytes due to acute inflammatory and prothrombotic state. PLR has been widely evaluated on a state of malignancy related to immune suppression and thrombosis, which can be predicted by the calculation of numbers and ratios. The MPV describes the platelet size and to find out platelet function. Platelet size in circulation is associated with inflammatory intensity. In some chronic inflammatory conditions, MPV is used as a chronic inflammatory marker of disease and monitoring of anti-inflammatory therapy.

The opioid is extensively used as an anesthetic agent on a wide range of operations. The opioid is used as an analytic and sedation. Besides, opioid also modulates immune responses through an opioid receptor that are directly expressed to the immune cell itself. Nowadays, the receptor of opioid kappa is believed to have a role in modulating various inflammatory conditions. The discovery of opioid receptors which are an expression in a variety of immune cells gives the idea that opioid has a direct effect on the immune system. Both endogenous and exogenous opioids affect the antibody’s response, cell-mediated immunity, phagocytosis, chemotaxis, neutrophil response, and mononuclear phagocytes. Opioid also

Table 1: Table of preoperative random blood sugar values and postoperative between groups remifentanil and fentanyl

| Blood sugar plasma preoperative (mg/dL) | Blood sugar plasma postoperative (mg/dL) |
|----------------------------------------|----------------------------------------|
| Group fentanyl                          |                                        |
| 1                                      | 74                                     | 1006                                   |
| 2                                      | 80                                     | 123                                    |
| 3                                      | 94                                     | 88                                     |
| 4                                      | 85                                     | 96                                     |
| 5                                      | 140                                    | 134                                    |
| Group remifentanil                      |                                        |
| 1                                      | 101                                    | 96                                     |
| 2                                      | 130                                    | 186                                    |
| 3                                      | 117                                    | 139                                    |
| 4                                      | 81                                     | 120                                    |
| 5                                      | 102                                    | 89                                     |
inhibits all phases of the HPA axis. In addition to suppressing the production of corticotropin-releasing hormone (CRH), opioid also lowers the sensitivity of pituitary anterior to the CRH. Opioid, especially remifentanil, may inhibit cortisol plasma according to the administered dose.[10-12]

This study shows no difference between remifentanil and fentanyl for inhibiting the increase of NLR and PLR from the baseline values. The remifentanil group is better in preventing the increase in postoperative PLR as compared to the fentanyl group. This is different from the research done by Lee et al. The another study proved that remifentanil was more effective in suppressing cytokines and oxidative stress response in cardiac surgery such as cardiopulmonary bypass.[13] In the previous study found remifentanil able to suppress increased IL-6, IL-8 da malondialdehyde after reopening aortic clamp is better than fentanyl. The activation of central opioid receptors provides an influence on the peripheral immune system through the stimulation of the sympathetic nervous system and lymphoid organs.

Among the various types of opioids, only remifentanil can inhibit the activation of neutrophil expose to the lipopolysaccharide by lowering the activation of inflammatory cytokines and p38 MAPKs in vitro. The suppression of neuroendocrine stress response by remifentanil during surgery also affects the functioning of the immune system, resulting in a good prognosis as long as the patient is done treatment in the intensive care unit.[14]

More research needs to be done with more sample quantities to see the effect of remifentanil on the response of the inflammation of surgery and perform other inflammatory marker examination.

**Conclusion**

In this study, there was no difference between the two groups in suppressing the increased marker of inflammatory stress response in postoperative. The remifentanil group is better in suppressing the platelet value to human ratio postoperation than that of the fentanyl group.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images, and other clinical information to be reported in the journal. The patients understand that their name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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