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Effects of various anaesthetic techniques on haemodynamic stability and inflammatory cytokine (IL-6) level in patients undergoing breast cancer surgery

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Abstract

Background: Different types of anesthesia have been shown to influence the balance of inflammatory cytokines to varying degrees, Anesthesia may modulate cancer growth and metastasis through directly influencing biological behaviors of cancer cells, or improving tumor microenvironment. Due to this we aim to evaluate the effects multimodal anaesthesia technique on level of IL-6 inflammatory cytokines in breast carcinoma surgery.

Materials and Methods: The present study was conducted in the Department of Anesthesiology of the MGM College, Navi Mumbai. For the study, we included patients with ASA grade I and II, age 18 to 65 years. Informed consent was obtained from all the patients. Patients were grouped randomly into three groups (n= 15 in each group). Group I: Received paracetamol as premedication 10 mg/kg and fentanyl at the time of induction 2 µg/kg and continued as normal general anaesthesia. Group II: Received paracetamol at 10 mg/kg and dexmedetomidine 0.5µg/kg as premedication and fentanyl at 2 µg/kg at the time of induction and continued as normal general anaesthesia. Group III: Received paracetamol 10 mg/kg and dexmedetomidine 0.5 µg/kg at the time of premedication and fentanyl at 2 µg/kg at time of induction and paravertebral block with levobupivacaine and continued as normal general anaesthesia.

Results: We observed that the mean age in group 1, group 2 and group 3 was 36.38 years, 39.25 years and 41.23 years, respectively. The mean weight of group 1, group 2 and group 3 patients was 61.38, 57.29 and 58.21 kg respectively. The duration of surgery was 112.39, 118.22 and 117.29 min, respectively for Group 1, 2 and 3. We observed that IL-6 levels decreased in all the groups. The decrease in IL-6 level postoperative was statistically significant for Group 3. The mean heart rate, at base line, induction time, intubation time and postoperative were not statistically difference in between all three groups.

Conclusion: Multimodal approach is a better anesthetic technique in terms of hemodynamic stability with decreased levels of IL-6 inflammatory cytokines.

Keywords: Cytokine, inflammation, haemodynamic, multimodal, paravertibral block

Introduction

Although various treatment methods such as chemotherapy, radiation therapy, and targeted therapy have been developed for the treatment of malignancies, surgical resection remains the most effective and the only radical treatment, especially for patients with early-stage disease^[1]. However, stress stimulations that arise during surgery may induce the abnormal synthesis of various inflammatory cytokines, thus inducing inflammatory responses, which can have a significant effect on both short-term adverse events and long-term treatment outcomes^[2]. Apart from surgical trauma, anesthesia used during surgery can also induce inflammatory responses. Different types of anesthesia have been shown to influence the balance of inflammatory cytokines to varying degrees^[3], Anesthesia may modulate cancer growth and metastasis through directly influencing biological behaviors of cancer cells, or improving tumor microenvironment^[4]. Compared to general anesthesia, regional anesthesia has been postulated to have positive effect on cancer outcome^[5]. Thoracic epidural anesthesia and analgesia have commonly been used for the management of intra- and postoperative pains during colon cancer surgery. General anesthesia and epidural anesthesia may suppress immunity via directly affecting the immune system or sympathetic nervous system^[6].

Hence, the present study was conducted to study the effects of various anaesthetic techniques on haemodynamic stability and inflammatory cytokine (IL-6) level in patients undergoing breast cancer surgery.

Materials and methods

The present study was conducted in the Department of Anesthesiology of the MGM College, Navi Mumbai. The ethical clearance for the study was approved from the ethical committee of the hospital. For the study, we included patients with ASA grade I and II, age 18 to 65 years. Informed consent was obtained from all the patients. Exclusion criteria were history of adverse reaction to any study medication, unstable cardiovascular disease, acute pulmonary diseases, history of analgesic use, history of heart block and hypertension, chronic pain syndrome were excluded from study. Patients were grouped randomly into three groups (n= 15 in each group). Group I: Received paracetamol as premedication 10 mg/kg and fentanyl at the time of induction 2 µg/kg and continued as normal general anaesthesia. Group II: Received paracetamol at 10 mg/kg and dexmedetomidine 0.5µg/kg as premedication and fentanyl at 2 µg/kg at the time of induction and continued as normal general anaesthesia. Group III: Received paracetamol 10 mg/kg and dexmedetomidine 0.5 µg/kg at the time of premedication and fentanyl at 2 µg/kg at time of induction and paravertebral block with levobupivacaine and continued as normal general anaesthesia. After completion of preoperative clinical assessment of patients was done keeping in mind the preoperative hemodynamic of patients. An intravenous access was established with 18 gauge cannula. Patients were monitored routinely with ECG, non-invasive blood pressure and pulse oximetry every 5 minutes for 15 minute and then every 15 minute till end of surgery. All patients were premedicated with inj. glycopyrolate 0.01mg/kg iv and inj. Ondansetron 0.1mg/kg iv. Paravertebral block was administered with 5 ml of 0.25% levobupivacaine at each level of T2, T4 and T6 thoracic vertebra of same operating side. Maintenance of anaesthesia was done with oxygen, N₂O, isoflurane and non depolarising muscle relaxant vecuronium. Residual paralysis was reversed with neostigmine and glycopyrrolate. The heart rate (HR), mean arterial pressure (MAP) and oxygen saturation were recorded at 15 minute regular interval till 2 hours post-operatively. Bradycardia was defined as heart rate.

The statistical analysis of the data was done using SPSS version 11.0 for windows. Chi-square and Student's t-test were used for checking the significance of the data. A p-value of 0.05 and lesser was defined to be statistically significant.

Results

The demographic profiles age, weight and duration of surgery of all three groups are shown in Table 1. We observed that the mean age in group 1, group 2 and group 3 was 36.38 years, 39.25 years and 41.23 years, respectively. The mean weight of group 1, group 2 and group 3 patients was 61.38, 57.29 and 58.21 kg respectively. The duration of surgery was 112.39, 118.22 and 117.29 min, respectively for Group 1, 2 and 3. The results on comparison were found to statistically non-significant. Table 2 shows the pre and post-operative IL-6 levels in all three groups. We observed that IL-6 levels decreased in all the groups. The decrease in IL-6

level postoperative was statistically significant for Group 3. The mean heart rate, at base line, induction time, intubation time and postoperative were not statistically difference in between all three groups ($p > 0.05$).

Discussion

In the present study, a total of 45 patients were assessed. We observed that IL-6 levels decreased in all the groups. The decrease in IL-6 level postoperative was statistically significant for Group 3. The mean heart rate, at base line, induction time, intubation time and postoperative were not statistically difference in between all three groups ($p > 0.05$). The results were compared with previous studies from the literature and were found to be statistically significant.

Deegan CA *et al.* [7] tested the hypothesis that patients who receive combined propofol/paravertebral anaesthesia-analgesia (propofol/paravertebral) exhibited reduced levels of protumorigenic cytokines and matrix metalloproteinases (MMPs) and elevated levels of antitumorigenic cytokines compared with patients receiving sevoflurane anaesthesia with opioid analgesia (sevoflurane/opioid). Primary breast cancer surgery patients were randomized to propofol/paravertebral (n = 15) or sevoflurane/opioid (n = 17) and preoperative and postoperative serum concentrations of 11 cytokines (interleukin 1β [IL-1β], IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-13, interferon γ, and tumor necrosis factor α) and 3 MMPs (MMP-1, MMP-3, and MMP-9) were measured. Treatment groups were well balanced for age, weight, surgical procedure, and cancer pathologic diagnosis. Pain scores were lower at 1 and 2 hrs with paravertebral analgesia compared with morphine but similar at 24 hrs. Patients in the propofol/paravertebral group showed a greater percentage decrease in postoperative compared with preoperative IL-1β (median [quartiles], -26% [-15% to -52%] versus -4% [-14% to 2%], $P = 0.003$), a significant attenuation in elevated MMP-3 (2% [-39% to 12%] versus 29% [23%-59%], $P = 0.011$) and MMP-9 (26% [13%-54%] versus 74% [50%-108%], $P = 0.02$), and a significant increase in IL-10 (10% [5%-33%] versus -15% [20% to -2%], $P = 0.001$) compared with sevoflurane/opioid group. No significantly different changes in IL-2, IL-4, IL-5, IL-6, IL-8, IL-12p70, IL-13, interferon γ, tumor necrosis factor α, or MMP-1 were observed between the 2 groups. They concluded that propofol/paravertebral anaesthesia-analgesia for breast cancer surgery alters a minority of cytokines influential in regulating perioperative cancer immunity. Further evaluation is required to determine the significance of these observations. Gürkan Y *et al.* [8] evaluated the analgesic effect of ultrasound-guided erector spinae plane (ESP) block in breast cancer surgery. Patients were randomized into two groups, ESP and control. Single-shot ultrasound (US)-guided ESP block with 20 ml 0.25% bupivacaine at the T4 vertebral level was performed preoperatively to all patients in the ESP group. The control group received no intervention. Patients in both groups were provided with intravenous patient-controlled analgesia device containing morphine for postoperative analgesia. Morphine consumption at postoperative hours 1, 6, 12 and 24 decreased significantly in the ESP group ($p < 0.05$ for each time interval). Total morphine consumption decreased by 65% at 24 h compared to the control group (5.76 ± 3.8 mg vs 16.6 ± 6.92 mg). There was no statistically significant difference between the groups in terms of NRS scores. Their study findings show that US-guided ESP block exhibits a

significant analgesic effect in patients undergoing breast cancer surgery.

Cho JS *et al.* [9] compared the effects of two different anesthesia and analgesia methods on the NK cell cytotoxicity (NKCC) in patients undergoing breast cancer surgery. Fifty patients undergoing breast cancer resection were randomly assigned to receive propofol-remifentanyl anesthesia with postoperative ketorolac analgesia (Propofol-ketorolac groups) or sevoflurane-remifentanyl anesthesia with postoperative fentanyl analgesia (Sevoflurane-fentanyl group). The primary outcome was NKCC, which was measured before and 24 h after surgery. Post-surgical pain scores and inflammatory responses measured by white blood cell, neutrophil, and lymphocyte counts were assessed. Cancer recurrence or metastasis was evaluated with ultrasound and whole body bone scan every 6 months for 2 years after surgery. The baseline NKCC (%) was comparable between the two groups ($P = 0.082$). Compared with the baseline value, NKCC (%) increased in the Propofol-ketorolac group [15.2 (3.2) to 20.1 (3.5), $P = 0.048$], whereas it decreased in the Sevoflurane-fentanyl group [19.5 (2.8) to 16.4 (1.9), $P = 0.032$]. The change of NKCC over time was significantly different between the groups ($P = 0.048$). Pain scores during 48 h after surgery and post-surgical inflammatory responses were comparable between the groups. One patient in the Sevoflurane-fentanyl group had recurrence in the contralateral breast and no metastasis was found in either group. They concluded that Propofol anesthesia with postoperative ketorolac analgesia demonstrated a favorable impact on immune function by

preserving NKCC compared with sevoflurane anesthesia and postoperative fentanyl analgesia in patients undergoing breast cancer surgery. Hou BJ *et al.* [10] investigated the influences of varied anesthetic methods and depths on inflammatory cytokines and stress hormone levels in radical operation among colon cancer patients during perioperative period. A total of 120 patients were collected in the study and randomly divided into 4 groups, A: general anesthesia + Narcotrend D1, B: general anesthesia + Narcotrend D2, C: general anesthesia + epidural anesthesia + Narcotrend D1, D: general anesthesia + epidural anesthesia + Narcotrend D2. The levels of tumor necrosis factor (TNF)- α , interleukin (IL)-6, IL-10, cortisol (Cor), adrenocorticotropic hormone (ACTH), and endothelin-1 (ET-1) were measured adopting commercial kits before anesthesia (T0), 4 hours after surgery (T1), 24 hours after surgery (T2), and 72 hours after surgery (T3). There was no significant difference in basic clinical characteristics among the groups. In comparison with group A, B and C, group D showed significantly lower levels of TNF- α , IL-6, IL-10, Cor, ACTH, and ET-1 at T1 and T2 (all, $P < .05$). Significantly higher levels of TNF- α , IL-6, IL-10, Cor, and ACTH were detected at T1 and T2 than those at T0 (all, $P < .05$), whereas, at T3, the levels of inflammatory cytokines and stress hormones were all decreased near to preoperation ones. They concluded that general anesthesia combined with epidural anesthesia at Narcotrend D2 depth plays an important role in reducing immune and stress response in patients with colon cancer from surgery to 24 hours after surgery.

Table 1: Demographic distribution of the patients

Variables	Group 1	Group 2	Group 3	p-value
Age (years)	36.38	39.25	41.23	0.221
Weight (kg)	61.38	57.29	58.21	0.31
ASA grade (I/II)	6/9	7/8	8/7	0.09
Duration of surgery (min)	112.39	118.22	117.29	0.65

Table 2: Pre and post-operative IL-6 levels in all three groups

	IL-6 (Pre-operative)		IL-6 (Postoperative)		p-value
Group 1	350.28	127.26	328.82	120.29	0.82
Group 2	349.36	131.25	315.32	118.87	0.29
Group 3	344.28	122.11	292.21	112.23	0.02

Conclusion

Within the limitations of the present study, it can be concluded that multimodal approach is a better anesthetic technique in terms of hemodynamic stability with decreased levels of IL-6 inflammatory cytokines. Thus, prevents inflammatory mediated tissue injury, organ dysfunction syndrome, postoperative mortality and prevents development of chronic persistent pain, ultimately leads to early mobilization and rehabilitation.

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