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

Introduction: Multimodal anaesthesia techniques include regional anaesthesia in the form of paravertebral block and various anaesthetic drugs which acts on different sites of pain pathway with different mechanism of action, results in good quality of analgesia with minimal side effects. They improve recovery along with early mobilization and rehabilitation and early resumption. This technique lowers the level of inflammatory cytokines. Due to this we aim to evaluate the effects multimodal anaesthesia technique on level of IL-6 inflammatory cytokines in breast carcinoma surgery.

Material and Methods: Patients were randomized into following three groups (n=30 in each group) using a computer generated random number tables. Group I: paracetamol 10 mg/kg, Group II: paracetamol at 10 mg/kg and dexmedetomidine 0.5µg/kg, Group III: paracetamol 10 mg/kg, dexmedetomidine 0.5 µg/kg and paravertebral block with levobupivacaine. Fentany (2 µg/kg) with general anaesthesia were common in all three groups. Statistical Analysis: All the categorical data was compared by using student "t" test, chi-square test and parametric data by analysis of variance (ANOVA).

Results: Patients of group III was haemodynamically more stable as compared to group II and I. IL-6 level was 358.15, in group I, 354 in group II and 346.65 in group III preoperatively while 324.85 in group I, 320.95 in group II, 278.35 in group III after 2 hour surgery. IL-6 level was significantly different in group III as compared to group II and group I postoperatively.

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

Breast cancer is the most common cancer and considered to be second leading cause of death in United States.[1-4] Cytokine IL-6 is a proproliferative, anti-apoptotic, pleiotropic biochemical marker which play an important role in the immune regulation, ontogenesis and inflammatory change caused by surgical trauma and stress.[5,6,7] Blockade or modulation of the IL-6 signal manifest clinically as diseases, including inflammation-associated malignancies is well on its way in clinical trials.[4,5,8]

Many modalities are used in treatment of breast carcinoma including surgical intervention. Surgery for management of breast carcinoma has many advantages although it has its neuro-endocrine, metabolic and cytokine responses that will affect the immune system according to their magnitude. Type of anesthesia used during these surgeries may augment these responses.[2,3]

General anesthesia (GA) is by far the most common utility used for breast surgeries. Regional anesthesia has the advantage of preventing noxious stimuli from reaching the central nervous system and therefore can attenuate the surgical stress response.[9] Drug commonly used in anaesthesia may modulate immunological reaction by inflammatory intracellular communication through modification of cytokine response and fluctuation of peripheral immune cells such as natural killer cell T- lymphocyte.[10]

Different anaesthetic method may interfere with the stress response especially cytokine activation during and after surgery. Breast surgery associated with increased level of inflammatory cytokine such as IL-1, IL-6, CRP which cause long lasting hyperalgesia.[2,11] These inflammatory cytokine alter pain signal transmitted by cytokine induced release of neuroactive substances such as nitric oxide oxygen free radical and excitatory amino acid.[3,12] Multimodal anaesthesia is defined as achievement of good quality of pain relief which is attained by through the synergistic effects of multiple drugs which act on different sites of pain pathway with different mechanism of action which lead to good quality of analgesia, minimizing doses of analgesics, reduced side effects, early mobilization and recovery, while general anaesthesia lead

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How to cite this article: Gajendra Pal Singh, Neel Kamal Mishra, Reetu Verma, Jitendra Kumar Kushwaha, Prithvi Kumar Singh, Wahid Ali, Nitu Nigam, Rajni Gupta, Jaishri Bogra, Anita Malik2, Rajni Kapoor. Effects of various anaesthetic techniques on haemodynamic stability and inflammatory cytokine (IL-6) level in patients undergoing breast cancer surgery. International Journal of Contemporary Medical Research 2019;6(8):H1-H5.

DOI: http://dx.doi.org/10.21276/ijcmr.2019.6.8.11

to tachycardia, hypertension, postoperative morbidity, poor pain control and other side effects due to use of excessive amount of opioids and inhalational agents.[13]

In present study various drugs used are fentanyl, paracetamol, dexmedetomidine, paravertebral block (PVB) along with general anaesthesia for patients undergoing breast cancer surgery. We hypothesized that multimodal anaesthesia technique had minimal effects on immune response ultimately lead to decreased incident of metastatic recurrence, development of chronic persistent pain with reduction of morbidity and mortality.

MATERIAL AND METHODS

This prospective comparative study was carried out after obtaining the approval from the institutional Ethical Committee. The patients of ASA grade I or II, age 18 to 70 years were included in this study. The study was carried in the department Surgical, K.G's Medical University between September 2014 to August 2015. 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 randomized into following three groups (n=30 in each group) using a computer generated random number tables.

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 gauze 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 anesthesia 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 <50 beats/min for which Inj. Atropine 0.01mg/kg was given. If mean arterial pressure was decreased ≥20% from baseline it was managed with fluid and ionotropic.

Venous blood samples of 3 ml were collected separately using aseptic precautions preoperatively and 2 hrs after surgery. Serum was aliquoted and stored at -20^{0}C until testing. Serum IL-6 level was determined by Ray bio human IL-6 ELISA kit which is an in vitro enzyme linked immunosorbent assay for the quantitative measurement of human IL-6 in serum. This assay employ an antibody specific for human IL-6 coated on a 96 well plates. Standard and samples are pipetted into the wells and IL-6 present in a sample is bound to the wells by immobilized antibody. The wells are washed and biotinylated anti human IL-6 antibody was added. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed, a TMB (tetramethylbenzidine) substrate solution is added to the wells and colour developed in proportion to the amount of IL-6 bound. The stop solution changed the colour from blue to yellow and intensity of colour is measured at 450 nm. All laboratory tests were conducted by the same staff was blinded to the clinical status of individual subject.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS 15.0 windows software. Comparisons between groups at different time intervals were assessed by using student "t" test. All the categorical data was compared by using chi square test. Parametric data was compared using analysis of variance (ANOVA). A p-value of < 0.05 was considered to be significant.

RESULTS

The demographic profiles age, weight and duration of surgery of all three groups are shown in Table 1 which included age (39.95±11.13, 40.05±11.33 and 45.00±11.82 years), weight (52.15±5.98, 51.30±5.59 and 51.80±5.51 Kg) and duration of surgery (109.50±18.91, 117.00±19.22 and 119.25±22.02) respectively. The demographic profiles age, weight and duration of surgery were not significantly different in between all three groups.

The mean heart rate, at base line, induction time, intubation time and postoperative were not statistically difference in between all three groups ($p > 0.05$) as shown in Fig. 1 and Fig. 2. However, heart rate was significant difference in between

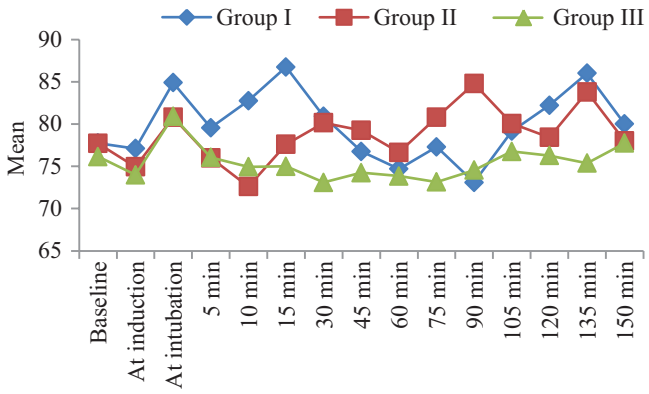

Figure-1: Heart Rate (Pre-operative and intra-operative)

	Group I (N=30)	Group II (N=30)	Group III (N=30)	p-Value
Age (years)	39.95±11.13	40.05±11.33	45.00±11.82	0.287
Weight (Kg)	52.15±5.98	51.30±5.59	51.80±5.51	0.894
ASA grade (I/II)	11/9	12/8	10/10	>0.5
Duration of surgery (min)	109.50±18.91	117.00±19.22	119.25±22.02	0.283

Table-1: Demographic distribution of the patients

	IL-6 (Pre-operative)		IL-6 (Postoperative)		p-Value
Group I	358.15	129.952	324.85	117.594	0.4008
Group II	354	135.83	310.95	115.523	0.2907
Group III	346.65	113.266	278.35	110.815	0.0414*
*Significant (p<0.05)					

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

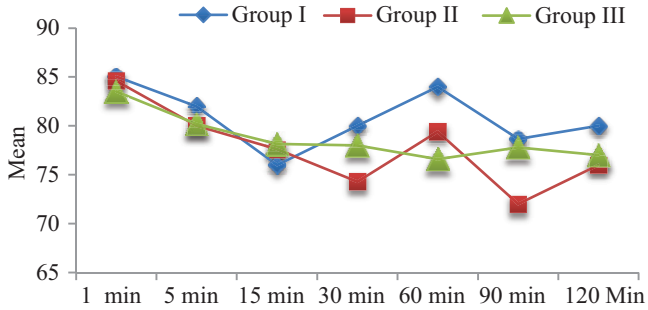

Figure-2: Heart Rate (Post-operative)

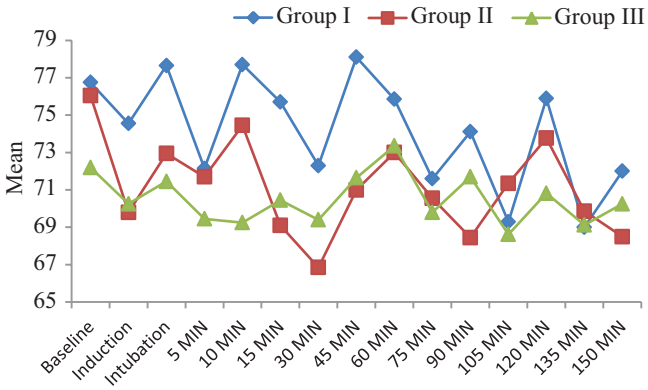

Figure-3: Mean arterial pressure (Pre-operative and intra-operative)

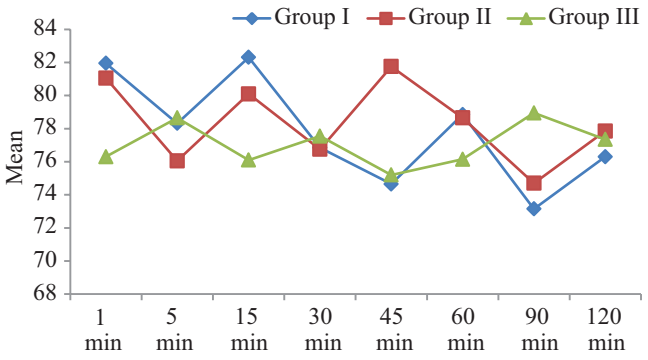

Figure-4: Mean arterial pressure (Post-operative)

all three groups at 5 min to 135 min. intra-operatively.

The mean arterial pressure at base line was not significant difference between all three groups (p >0.05). Whereas mean arterial pressure at induction time and intubation time were significant difference (p<0.05). It was significantly different at 10 min, 15 min, 30 min, 75 min and 105 min, intraoperatively (Fig. 3) and 1 min, 5 min, 15 min and 45 min postoperatively (Fig. 4).

Pre and post-operative IL-6 levels was summarized in Table 2. In group I and group II the IL-6 level was not significant difference between pre and post-operative. However, in group III the IL-6 level was significant difference between pre and post-operative.

DISCUSSION

The regional anesthesia and analgesia may help to preserve immune function by attenuating the surgical stress response, reducing anesthetic requirement and decreasing the needs for opioids.[16] Local anesthetics inhibit release of inflammatory mediators and block receptors for them. They are also able to down regulate processes involved in immune cell trafficking like adhesion and transmigration, resulting in lesser accumulation of the cells at the injury site.[17] The immunosuppressive alterations in lymphocyte subsets induced by surgery and general anesthesia can be prevented to certain degree by epidural anesthesia paravertebral block.[18] Cytokines have a significant role in acute inflammatory and immune responses initiated by surgery, trauma, infection or malignancy. They have local and systemic effects aiming to limit tissue injury and spread of infection.[18] They also provoke tissue healing and repair. After surgery, main cytokines released are IL-1, TNF-α, IL-6, the latter being responsible for inducing systemic changes known as acute phase response. They can be used as biomarkers reflecting the magnitude of stress accompanying the surgical management.[18] The systemic inflammatory response likely depends on the invasiveness of the surgical procedure. Although the nature of cytokine response is determined by surgical trauma, the anesthetic and analgesic technique is capable of modifying its extent.[18] Pain control during as well as after breast surgery is very important, it prevents comorbidities, thus lead to early mobilization and rehabilitation. Paravertebral blockade has been shown to be a classical multimodal analgesic technique. In our study the mean heart rate was not significantly different between groups at base line, during induction, intubation and in postoperative period. However, heart rate was significantly different at 5 min to 135 min. intraoperatively in all three groups. Similarly, Jain et al. (2009) found that the bolus

dose of dexmedetomidine was associated with significant fall in heart rate 7-10 minutes after the start of bolus, but no intervention was required as the fall was transient and did not affect blood pressure.[19]

In our study, Group II and Group III were associated with slight fall in heart rate after 5 minutes of intubation. But none of the patient had clinically significant hypotension nor needed any treatment. This can be because in our study, loading dose of dexmedetomidine 0.5µg/kg was given in 100 ml normal saline over 10 minutes. After single injection of unilateral of PVB given at the level of T4, as a sole anaesthetic technique for CA breast, none of patient had any episode of hypotension and the hemodynamic parameters were comparable between the two groupsregional anaesthesia vs general anaesthesia.[20] The sympathetic changes following unilateral PVB with lidocaine at T11 spine and demonstrated that PVB provides a reliable, unilateral, somatosensory and sympathetic block without producing hypotension and tachycardia associated with neuraxial blocks.[21] During the intraoperative period, regional neuraxial blockade with general anaesthesia was significantly lower the mean arterial blood pressure (MAP) and pulse rate.[22] Tomar et al. (2015) found that haemodynamic stability was significantly greater in dexmedetomidine along with fentanyl and PCM as compared to fentanyl and PCM group.[23]

In the present study we observed that the IL-6 level was significantly different between pre and post-operative in group III whereas, it was not significantly different between group I and group II. Similary, Li et al. (2014) reported that the perioperative use of dexmedetomidine as an adjunct substantially decreases serum IL-6 levels.[24] The IL-6 level was significantly reduced in regional neuraxial blockade group as compared to general anaesthesia group.[22] According to Kuo et al. (2006) regional neuraxial blockade group had better postoperative pain relief and the least cytokine surge as compared to intravenous groups (iv).[25]

CONCLUSION

Present study concludes 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. Although additional studies with larger sample sizes will be necessary to confirm our findings.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 15-06-2019; **Accepted:** 10-07-2019; **Published:** 10-08-2019