Paravertebral block can attenuate cytokine response when it replaces general anesthesia for cancer breast surgeries

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ABSTRACT

Context: Cytokine release is a well-known response to surgery especially when it is linked to cancer. Paravertebral block (PVB) is the suitable regional anesthesia for breast surgery. **Aim:** We tested the effect of replacing general anesthesia (GA) with PVB on cytokine response during and after surgeries for cancer breast. **Settings and Design:** Controlled randomized study. **Methods:** Forty cancer breast patients were divided in two groups; Group I received PVB and Group II received GA during performance of unilateral breast surgery without axillary clearance. Plasma concentrations of interleukin (IL)-6, IL-10, IL-12 and interferon-γ (IFN-γ) were measured and IL-10/IFN-γ were estimated in the following points; before starting PVB in Group I or induction of GA in Group II (Sample A), before skin incision (Sample B), at the end of procedure before shifting out of operating room (Sample C), 4-h post-operatively (Sample D) and 24-h post-operatively (Sample E). **Statistical Analysis:** unpaired Student *t*-test. **Results:** IL-6 increased progressively in both groups with statistically significant lower levels in samples C and D in Group I. IL-10 levels showed progressive increasing in both groups without differences between groups. IL-12 showed progressive decrease in both groups with statistically significant higher levels in samples C and D in Group I. IFN-levels showed significantly higher levels in samples C and D in Group I. IL-10/IFN-γ ratio was significantly lower in Group II in samples C and D. **Conclusion:** Replacing GA with PVB can attenuate cytokines response to cancer breast surgeries.

Key words: *Cancer breast, interleukins, paravertebral block*

INTRODUCTION

Breast cancer is the most common cancer diagnosed in US women. It is considered as the second leading cause of death from cancer in US women.[1] Many modalities are used in treatment of cancer breast including chemotherapy, radiotherapy and surgical intervention. Surgery for management of cancer breast has many advantages although it has its neuro-endocrine, metabolic and cytokine responses that will affect the immune system according to their magnitude.[2] Type of anesthesia used during these surgeries may augment these responses.[3]

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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.[4] Thoracic paravertebral block (PVB) proved efficacy as a lone anesthesia regimen for breast surgery.[4-7]

Proinflammatory cytokines (e.g., tumor necrosis factor (TNF), interleukin (IL)-1 (IL-1), (IL-2), (IL-6), (IL-7) and (IL-12)) and anti-inflammatory cytokines (e.g., (IL-4) and (IL-10)) have a crucial role in immune defense. Cytokines are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis. Cytokines generally function as intercellular messenger molecules that evoke particular biological activities after binding to a receptor on a responsive target cell. Their release is largely affected by a wide variety of physiological and pathological entities.[8] The aim of this study is to investigate the effect of PVB on cytokine response to surgical interventions of cancer breast when compared with GA.

METHODS

This Controlled randomized study was done after obtaining approval of Research Ethics Committee, Faculty of Medicine, Ain Shams University. The study enrolled 40 female patients, ASA physical status I or II with cancer breast scheduled for unilateral breast surgery without axillary clearance. Written consents were obtained from all patients. Exclusion criteria included age below 18 years old, obesity (body mass index (BMI) > 35), pregnancy, lactation, known allergy to bupivacaine or any contraindication to PVB (history of bleeding disorder, kyphoscoliosis or herpes zoster). Patients were randomly assigned to one of two groups. Group I received PVB and Group II worked as a control group and received GA.

Patients in Group I were sedated during performance of PVB with midazolam 0.03-0.06 mg/kg and fentanyl 1-2 mcg/kg. During the surgical procedure, propofol infusion was used in a dose of 25-75 mcg/kg/min. PVB was performed with the patient in lateral position (surgical side facing upward). Spinous processes of T3 to T6 were identified. A mark was taken corresponding to 2.5 cm lateral to them. These points were infiltrated with lidocaine 1%. In each of these points, a tuohy needle was inserted perpendicular to the skin. On touching the corresponding transverse process, the needle was withdrawn and redirected to reach a depth of 4 cm as a maximum. A loss of resistance to saline was usually encountered at this depth. At that point, a 5 ml of 0.5% bupivacaine was injected. This was repeated with the four chosen points. Sensory loss was tested 30 min later and surgery started after which. If sensory loss was not satisfactory the patient was given GA and excluded from the study. Verbal contact was kept with all patients and standard monitors were applied to all patients.

Patients in Group II received no sedation. Induction of anesthesia was done by 1 mcg/kg fentanyl, 2-3 mg/kg propofol and 0.15 mg/kg cisatracurium. Anesthesia was maintained with 1-2% sevoflurane in 50% N_2O in O_2 and incremental doses of fentanyl (to a maximum of 4 mcg/kg) and cisatracurium.

Blood samples were withdrawn in 5 times; before starting PVB in Group I or induction of GA in Group II (Sample A), before skin incision (Sample B), at the end of procedure before shifting out of operating room (Sample C), 4-h post-operatively (Sample D) and 24-h post-operatively (Sample E). Samples were collected as 10 ml sample in heparinized syringes before getting centrifuged and stored at 4°C until assayed. The following cytokines were measured; (IL-6), (IL-10), (IL-12) and interferon-γ (IFN-γ). The analytic methods utilized enzyme-linked immunosorbent assays strictly as described by the manufacturer's instructions (Pharmingen, San Diego, CA, USA). Both the nurse responsible for samples collection and the laboratory staff responsible for samples procession were blinded to which group the patient were belonging to.

Statistical analysis was performed using SPSS windows version 15 (SPSS Inc., Chicago, IL., USA). Data comparing results in two groups were compared with unpaired Student *t*-test. A value of $P<0.05$ was considered to be statistically significant.

RESULTS

No significant differences were detected between the two groups concerning age, weight, height, BMI and duration of surgery [Table 1].

Changes in cytokines levels are listed in Table 2. IL-6 increased progressively in both groups. There were statistically significant lower levels of IL-6 in samples C and D in Group I when compared with Group II. IL-10 levels showed a progressive increase in both groups without differences between groups. IL-12 showed progressive decrease in both groups. There were statistically significant higher levels of IL-12 in samples C and D in Group I compared with Group II. IFN-γ levels showed significantly higher levels in samples C and D in Group I when compared with Group II. IL-10/IFN-γ ratio was significantly lower in Group II in samples C and D when compared with Group I.

DISCUSSION

PVB has been studied as an alternative to GA during breast surgery. Results of most of the studies showed that PVB is capable of inducing lower post-operative pain, lower incidence of post-operative nausea and vomiting and shorter hospital stay.[4,5,9-11] It has been proposed that by blocking pain pathways, PVB can reduce acute stress response caused by surgery.[4]

Table 1: Demographic data and duration of surgery

	Group I	Group II
Age (years)	42.2 (13.4)	40.4 (14.3)
Weight (kg)	72.6 (12.8)	69.9 (14.3)
Height (cm)	162.4 (10.5)	164.3 (11.5)
BMI (kg/m²)	27.4 (0.1)	26.9 (0.1)
Duration of surgery (min)	84.6 (18.4)	86.4 (19.6)

BMI – Body mass index; Data were expressed as mean (SD)

Table 2: Plasma concentration of measured cytokines in the two groups in pg/ml

	Group I					Group II				
	Sample A	Sample B	Sample C	Sample D	Sample E	Sample A	Sample B	Sample C	Sample D	Sample E
IL-6	8.4 (2.1)	8.6 (2.0)	32.9 (12.6)*	67.3 (22.3)*	105.2 (32.6)	8.9 (1.9)	8.7 (2.3)	43.7 (16.7)	88.4 (26.2)	121.1 (40.2)
IL-10	14.1 (6.2)	14.3 (6.3)	16.1 (7.8)	17.1 (8.6)	19.2 (9.3)	11.9 (5.1)	12.4 (5.4)	15.9 (7.6)	19.1 (8.6)	20.4 (9.8)
IL-12	345.3 (102.4)	331.9 (104.3)	309.3 (89.5)*	298.1 (67.8)*	213.4 (52.2)	338.4 (108.8)	334 (100.3)	259.1 (59.7)	248.4 (52.3)	198.3 (33.2)
IFN-γ	38.1 (17.4)	37.9 (16.9)	34.8 (15.9)*	31.9 (14.6)*	34.2 (15.6)	35.8 (16.4)	33.0 (15.4)	23.2 (10.5)	20.9 (9.3)	32.8 (15.2)
IFN-γ/IL-10	2.7 (1.2)	2.6 (1.2)	2.2 (1.0)*	1.9 (0.8)*	1.8 (0.8)	3.0 (1.4)	2.6 (1.2)	1.4 (0.6)	1.1 (0.5)	1.6 (0.7)

*Statistically significant; Data were expressed as mean (SD); Sample A – Before starting PVB (Group I) or induction of GA (Group II); Sample B – Before skin incision; Sample C – At the end of procedure before shifting out of operating room; Sample D – 4-h post-operatively; Sample E – 24-h post-operatively; IFN-γ – Interferon-γ; IL – Interleukin

The overall response to stress in its different modalities (whether due to surgery, trauma or malignancy) is immunosuppressive. This action aims mainly to protect the human body, but in further advancement it would be harmful. Impairment of the immune system response is seen in many views post-operatively. These include post-operative higher rate of infection and depression of the bone marrow.[12]

Surgical trauma induces a decreased cell-mediated immunity. This is due to impaired natural killer cell response and T helper 1 (Th1) lymphocyte development, which may results in a preferential Th2 development. This is responsible for post-operative increase in plasma concentrations of Th2 cytokines.[13]

Cytokines have an important role in acute inflammatory and immune responses initiated by trauma, surgery, malignancy or infection. They have local and systemic effects aiming to limit tissue injury and spread of infection. They also provoke tissue healing and repair.[14] They can be used as biochemical markers reflecting the magnitude of stress accompanied the surgical manipulation. Higher levels of IL-6 were reported in open versus laparoscopic surgeries.[15] Knowing that higher levels of IL-6 are linked to a higher incidence of post-operative complications[16] indicates that some cytokines could serve as a marker for the outcome after stressful conditions.

IL-6 is primarily responsible for the hepatic response, resulting in the synthesis of acute phase proteins and C-reactive protein, activation of immunosuppressive cytokines such as IL-10 and hematopoiesis.[17] IL-10 down-regulates the expression of Th1 cytokines. IL-10 is capable of inhibiting the synthesis of proinflammatory cytokines like IFN-γ. It also displays a potent ability to suppress the antigen-presentation capacity of antigen presenting cells; however, it is also stimulatory toward certain T cells and mast cells and stimulates B cell maturation and antibody production.[18] IL-12 is known as a T cell-stimulating factor, which can stimulate the growth and function of T cells. It stimulates the production of IFN-γ and TNF-α. IL-12 mediates enhancement of the cytotoxic activity of many cells. IL-12 also has anti-angiogenic activity (by increasing production of IFN-γ) and was tried as an anti-cancer drug.[19] IFN-γ is critical for innate and adaptive immunity against viral and intracellular bacterial infections and for tumor control through its immunostimulatory and immunomodulatory effects.[20]

Perioperative immune response is affected by multiple factors including surgical and anesthetic plans taken during performance of the procedure. Many anesthetic techniques are used to decrease immune responses to surgeries.[11,21-25] Regional anesthesia plays a major role in attenuating stress responses during surgeries[26-32] and may consequently affect the overall outcome of patients. PVB is the suitable regional anesthetic technique for breast surgery when performed in upper thoracic area. Retrospective analysis suggests that paravertebral anesthesia and analgesia for breast cancer surgery reduces the risk of recurrence or metastasis during the initial years of follow-up.[3]

Surgical stress is known to induce an increase in serum levels of IL-6, IL-10 and a decrease in serum levels of IL-12 and IFN-γ.[32] The present study proved these results. Both groups showed changes of serum levels of these ILs in the same direction with higher degrees of changes in Group II that received GA and worked as a control group. The maximum ability of PVB in attenuation of these changes was in samples C and D. This reflects that the maximal effect of PVB was at the immediate post-operative period and up to 4 h later. In the present study, PVB was not extended to the post-operative period by the utilization of a catheter technique in the paravertebral space. This may explain insignificant differences between groups 24-h post-operatively.

Attenuation of changes in IFN-γ and IL-10 in samples C and D in Group I resulted in significantly higher IFN-γ/IL-10 ratio in this group when compared with Group II. The IFN-γ/IL-10 ratio is expected to decrease with stressful conditions. It has been described with whole body hyperthermia,[33] during aerobic exercise[34] and even during the psychological stress.[35,36] It has been

hypothesized that high IFN-γ/IL-10 ratio is necessary for the control of infection.[37] Decrease in serum levels of IFN-γ is highly linked to infections especially viral.[38] Maintaining higher levels of IFN-γ perioperatively is an important goal especially in immunocompromised patients like cancer patients.

CONCLUSION

In conclusion, replacement of GA with PVB for surgeries of cancer breast is accompanied with an attenuation of cytokine response to surgery. Further studies still needed to study if this effect could be extended beyond immediate post-operative period by utilizing a catheter technique inside the paravertebral space.

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