ORIGINAL RESEARCH   **REGIONAL ANESTHESIA**

Evaluation of the effects of the local anesthetics on immunity during mastectomy

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ABSTRACT

Background & objective: Surgery and some anesthetic techniques can contribute to tumor cells dissemination. It is known that the use of local anesthetics and regional blocks during mastectomy preserved the immune function. We evaluated and compared, the levels of some cytokines (IFNγ, TNFα, IL2, IL12) responsible for immune function, as well as the level of leukocytes before and after breast carcinoma surgery; and to find out and compare the effects of local anesthetics on blood pressure (BP) and on postoperative complications, e.g., pain, vomiting, headache, the need for analgesia and surgical complications.

Methodology: In this randomized prospective study, 45 patients were allocated in 3 equal groups: Group GA (n = 15) for standard general anesthesia; Group LA (n = 15) for general anesthesia and infusion of lidocaine; Group PECS (n = 15) for pectoralis I/II block with bupivacaine and general anesthesia. Blood samples were taken to ascertain cytokines and leukocytes levels before surgery and 24 h after surgery.

Results: Lidocaine caused fall of BP (P = 0.002t), but bupivacaine (PECS I/II block) produced stable BP during mastectomy (P = 0.1). A significant increase of leucocytes after surgery was seen in Group PECS compared to Group GA (P = 0.033). In 24-h intervals after surgery, lidocaine and bupivacaine produced an increase of TNFα (P < 0.05). Bupivacaine showed a significantly low intensity of postoperative pain compared to other techniques and zero postoperative complications.

Conclusion: Local anesthetics lidocaine and bupivacaine enhance the immune response and produce more stable hemodynamics compared to general anesthesia alone during mastectomy in patients with breast carcinoma.

1. INTRODUCTION

Surgery is the gold standard treatment for breast carcinoma.[1,2] Radical mastectomy and its modified approaches have offered best results for patients' survival in the long-term.[3] However, the surgical manipulation in the tumor surroundings leads to dissemination of the tumor cells across the blood and lymphatic system, causing recidivism and distant metastasis.[4,5] Recent knowledge from literature shows that some anesthetics and anesthetic techniques can modify this course of the tumor cells.[6]

Surgical trauma produces severe stress response in the tissue of the body, releasing stress mediators: catecholamines, prostaglandins, cortisol, cytokines, and others.[6] All of them produce immuno-suppression with diminished cellular immunity. Immunity is one of the key factors involved in the long-term prognosis of breast carcinoma patients.[7]

Natural killer cells (NKCs) are the first line of defense in the body from dissemination of the tumor cells. Their activity is crucial, but some studies show that surgery, volatile anesthetics, and opioids decrease the activity of the NKCs, cytotoxic T lymphocytes (CTLs), and the ratio of Type 1 T helper (Th1) cells / Type 2 T helper (Th2) cells. CTLs can directly eliminate the tumor cells. Interferon Gamma (IFNγ), Tumour necrosis factor α (TNFα), Interleukin-2 (IL2), Interleukin-12 (IL12) are indicators of produced CTLs.[8]

It has been shown that isoflurane, sevoflurane and desflurane suppress the cytotoxicity of the NKCs and provoke tumor growth, but the use of propofol for anesthesia has a positive impact on the immune function.[8,9] It does not change the activity of the NKCs and the ratio of Th1/Th2.[10]

Over the past years interest has increased regarding the peroperative use of local anesthetics during mastectomy and their effects on immunity. It is well known that regional anesthesia blocks the afferent and efferent nerves stimulations, suppresses the activation of the sympathetic nervous system, and decreases the activity of HPA axes.[11] These effects make local anesthetics to be known as anti-tumor agents.[12]

Hitherto, the positive effects of lidocaine have been proved and confirmed *in vitro*, associated with reduction of tumor proliferation, migration, and invasion of cancer cells.[10]

The hypothesis that perioperative use of lidocaine or bupivacaine may decrease the surgical stress, inflammatory reaction, and immunity, the levels of leukocytes and cytokines responsible for cell immunity was the subject of our study.

Objectives of the study

The primary objective of the study was to evaluate, pre- and post-surgery, levels of cytokines (IL2, IL12, IFN-γ), TNFα and leukocytes, when local anesthetics were used during breast surgery (as peroperative infusion), or as pectoralis (PECS) I/II block, and to compare the findings with those estimated in standard general anesthesia (GA) for mastectomy.

The second objective was to find out and compare the effects of the use of combined anesthesia in breast surgery *vs.* standard GA alone for breast surgery on blood pressure and postoperative complications (pain, vomiting, headache, the need for analgesia and surgical complications).

2. METHODOLOGY

This randomized prospective study was conducted at the Department of Anesthesia, Thoracic and Vascular Surgery, University Clinic for Traumatology, Orthopedics, Anesthesia, Reanimation and Intensive Care and Emergency Center (TOARICEC), at the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia.

After obtaining the approval for the study by the Ethics Committee of Medical Faculty at UKIM (No 03-2529/5; 08.06.2022), 45 patients admitted for mastectomy for breast carcinoma, meeting the inclusion criteria, were enrolled in the study.

Patients who were conscious and communicative, with beast carcinoma, aged 16 to 80 y, ASA I-III, BMI < 35 kg/m^2, without previous therapy such as radiation or hemotherapy and who signed written agreement to be included in the study, were included. After the preoperative assessment in the outpatient clinic, patients were randomly allocated to one of the study groups by selecting one of the sealed envelopes. Oral premedication was given to each patient (1 mg midazolam one hour before surgery) and Visual Analogue Scale (VAS) was explained. One day prior to surgery, and 24 h after surgery a whole blood sample (5 ml) was taken to analyze leukocytes levels and the cytokines (Luminex® 200).

Continuous perioperative noninvasive monitoring and four measurements of hemodynamic parameters, BP, pulse rate, continuous ECG, SpO$_2$, EtCO$_2$ and Bi-spectral index (BIS), were performed for all patients (using Datex Ohmeda monitoring system). The timing was: T1: before the induction to anesthesia (ITA), T2: 10 min after ITA, T3: 30 min after ITA.

The patients for Group GA (n = 15, control group), after a verified vein line and preoxygenation, were induced GA with fentanyl 0.002 mg/kg, propofol 2 mg/kg, and rocuronium 0.6 mg/kg were given. After the intubation, anesthesia was maintained with additional doses of fentanyl and muscular relaxant; patients were mechanically ventilated with a mixture of oxygen and air (50 Vol% each), pressure-controlled ventilation; TV 6-8/kg and PEEP 5 cmH$_2$O. According to the depth of anesthesia, additional doses of opioids were given.

The patients in Group LA (n = 15), received lidocaine in a bolus of 1 mg/kg IV prior to induction to standard GA and an infusion of 1 mg/kg/h lidocaine applied by perfusor immediately after the surgical cut, stopped at the end of the surgery and anesthesia.

The patients for Group PECS (n = 15) received PECS I/II block, with 0.25% bupivacaine 0.2 ml/kg, which was applied under ultrasound guidance in two areas for anesthesia of the pectoralis minor, pectoralis major, and serratus, and when the analgesia was accomplished, patients were introduced to GA with propofol and relaxant if it was necessary. The need for analgesics was noted.

The same postoperative protocol was applied in all studied groups. All patients were admitted to the postanesthetic care unit (PACU). Thirty minutes after the end of the operation, patients were tested for the presence and degree of the pain (VAS), need for analgesia, vomiting, shivering, headache, and agitation. The level of pain was tested in 4-time intervals (T0 - 30 min after anesthesia, T1 - 6 h postoperatively, T2 –24 h after surgery and T3 - 48 h after surgery. Control blood samples were taken 24 h after surgery.

Statistical analysis

The obtained data of the study were statistically analyzed, with SPSS software package, version 20.0 for Windows (SPSS, Chicago, IL, USA). The Shapiro-Wilk W test was used for regular distribution and Mann Whitney U test for data with irregular distribution. Proportions were analyzed with a Difference test. P < 0.05 was considered statistically significant.

3. RESULTS

The results obtained in this study are presented in tables. The total number of examined patients was 45, with 15 patients in each of the three groups. The patients' characteristics and duration of the surgery among the groups were consistent and homogeneous (P > 0.05) (Table 1).

Table 2 illustrates the results of the studied cytokines obtained from the blood samples prior to surgery and 24 h after surgery. The pre-operative values of IFNγ, TNFα, IL2, IL12 in groups are similar and without statistically significant difference.

In groups with local anesthetics (Group L and Group BG) in the 24 h interval after surgery, an increase of TNFα was seen, with a statistically significant difference (P < 0.05). The other studied parameters, IFNγ, IL2 and IL12, showed no significant difference in the pre- and 24 h post-operative values (P > 0.05).

The changes regarding leucocytes, neutrophil and lymphocyte counts are presented in Table 3. The total WBCs (TLC) levels in the Group GA had the tendency of change but without statistical significance. In the Group LA, 24 h after surgery, a significant increase of

Table 1: Demographics of patients and duration of surgery and anesthesia

Variables	Group GA (n = 15)	Group LA (n = 15)	Group PECS (n = 15)	P-value
Sex (F/M)	15/0	15/0	15/0	NS
Weight (kg)	58.6 ± 9.5	59.3 ± 6.5	59.6 ± 7.6	
Timing of surgery (min)	73.4 ± 10.9	63.4 ± 15.5	61.7 ± 10.5	
Duration of anesthesia (min)	75.7 ± 12.0	77.3 ± 19.0	73.6 ± 11.2	
*F-female, M-male, BW-Body weight; *P < 0.05 – significant difference*				

Table 2: Levels of TNFα, IFN γ, IL 2 and IL12 in groups pre- and 24h post-surgery

Variables	Group GA (n = 15)	Group LA (n = 15)	Group PECS (n = 15)	P
TNFα (pre-op)	1.2 ± 0.2	1.8 ± 0.9	1.8 ± 0.9	NS
TNFα (24 h post-op)	1.3 ± 0.2	2.4 ± 1.5*	2.4 ± 1.5*	< 0.05
IFNγ (pre-op)	18.4 ± 9,7*	13.6 ± 2	13.1 ± 1.4	> 0.05
IFNγ (24 h post-op)	17.0 ± 7	13.5 ± 0.9	13.7 ± 0.6	NS
IL2 (pre-op)	0.6 ± 0.06	0.67 ± 0.12	0.65 ± 0.08	
IL2 (24 h post-op)	0.63 ± 0.05	0.5 ± 0.04*	0.67 ± 0.07	NS
IL12 (pre-op)	47.4 ± 5.8	44.08 ± 2.7	47.03 ± 2.1	
IL12 (24 h post-op)	47.0 ± 5.2	46.1 ± 3.4	45.5 ± 4.9	NS

*Cytokines quantifications by Luminex ® 200 platform, presented in pg/μL; *P < 0.05 – significant difference*

Table 3: Levels of leucocytes, neutrophils and lymphocytes pre- and 24 h post-surgery

Group	Leuco 1	Leuco2	Neutro 1	Neutro 2	Lympho 1	Lympho 2
Group GA	8.8 ± 2.5	9.7 ± 3.4	6.6 ± 2.7	7.16 ± 2.8	2.6 ± 0.9	2.2 ± 0.7
P =	0.46		0.607		0.255343	
Group LA	6.7 ± 1.2	8 ± 2.6	3.6 ± 1.1	5.3 ± 1.3	2.1 ± 0.4	2.2 ± 0.9
P	0.11		0.012		0.871519	
Group PECS	7.2 ± 2.4	9.3 ± 2.7*	4.8 ± 1.8	6.9 ± 2.2*	2.2 ± 0.9	1.9 ± 0.9*
P	0.03		0.007599		0.452717	
Inter-groups (ig) P =	1:2 = 0.0077 1:3 = 0.09		1:2 = 0.06 1:3 = 0.03		1:2 = 0.15 1:3 = 0.3	
(ig) After 24 h P	1:2 = 0.13 1:3 = 0.033		1:2 = 0.06 1:3 = 1.8		1:2 = 0.93 1:3 = 0.384	

*WBC measurement - leucocytes – 103 mm3; neutrophils - 1103 mm3; lymphocytes- 103 mm3. *P < 0.05*

Table 4: Blood pressure (BP) in mmHg in three-time intervals in the groups

GROUP	BP 1	BP 2	BP 3	p
Group GA (n = 15)	151 ± 21/83 ± 8*	127 ± 20/77 ± 1	124 ± 16/72 ± 1	P = 0.02
Group LA (n = 15)	140 ± 14/81 ± 9	117 ± 7/71 ± 6*	123 ± 8/72 ± 4	P = 0.002
Group PECS (n = 15)	145 ± 13/81 ± 6	136 ± 14/78 ± 7	133 ± 11/77 ± 8	NS
P (1:2; 1:3)	P = 0.15	P = 0.02*	P = 0.1	

*BP1 – before induction, BP2 – 10 min after induction, BP3 – 30 min after induction; *P < 0.05*

neutrophils (P = 0.012) was seen. PECS I/II blocks produced an increase of leucocyte and neutrophil counts (P = 0.03 and 0.007), and a slight decrease of lymphocytes (P = 0.4).

The perioperative hemodynamics in the study groups were continuously followed by monitors. The preoperative values of the mean systolic and diastolic pressures (BP1) were statistically insignificant between the groups (P = 0.15); however, there was significant fall of BP 10 and 30 min after induction of GA (P = 0.02); a

statistically significant fall in the Group LA (P = 0.002) and a stable BP without significant changes in the Group PECS (P = 0.1) (Table 4).

The degree of pain was measured with the Visual Analogue Scale (VAS) four times: T1, T2, T3 and T4 (Table 5). At T1, the pain scores in Group PECS compared to Group GA and Group LA were significantly lower (P = 0.05). In T2 a statistically significant difference (P = 0.05; P = 0.03) in Group LA and Group PECS, compared to Group GA was found (Table 5).

Table 5: Postoperative pain scores measured with visual analogue scale in the groups

Timing	Group GA (n = 15)	Group LA (n = 15)	Group PECS (n = 15)	p
T1	3.5 ± 1.2	3.7 ± 1.1	1.1 ± 1.1*	0.05
T2	3.7 ± 2.4	1.8 ± 0.4*	1.2 ± 0.9*	0.03
T3	0.4 ± 0.7	0.7 ± 0.9	0.6 ± 0.8	NS
T4	0	0	0	NS

*T1 – after awakening; T2 – 6h after surgery; T3-24 h after surgery; T4-48 h after surgery; *P < 0.05*

Table 6: Postoperative complications and dose of used opioid

Variables	Group GA (n = 15)	Group LA (n = 15)	Group PECS (n = 15)	p
POVN	4 (26.6%)	4 (26.6%)	2 (13.3%) *	< 0.05
Headache	4 (26.6%)	1 (6.6%) *	2 (13.3%) *	< 0.05
Fentanyl (ml)	5.8 ± 0.8	4.6 ± 0.8	2.06 ± 0.35*	< 0.05
Surgical complications	2 (13.3%)	1 (6.6 %)	0	

*PONV - postoperative nausea and vomiting; *P < 0.05*

The postoperative complications PONV and headache, the quantity of used fentanyl and surgical complications are presented on Table 6. The intergroup analysis of the data showed a statistically significant difference between appearances of POVN, headache, the quantity of used fentanyl and surgical complications, between the Group PECS compared to Groups GA and Group LA (P < 0.05).

Regarding the rate of complications, there was a significant difference between Groups GA and Group PECS (13,33% vs 0%; P < 0.05) and between Group LA and Group PECS (6.6% vs 0; P < 0.05), in contrast to Groups GA and Group LA (13.33% vs 6.6%) which were not significant. In Group PECS no complication was registered.

4. DISCUSSION

There is clinical and experimental evidence that anesthesia and surgery can affect the immune function.[1] Surgery and surgical manipulation lead to an increase of the interleukins of inflammation. Its activity decreases the apoptosis producing immunosuppression and tumor development.[6] The volatile anesthetic agents, such as isoflurane, sevoflurane, and desflurane, as well as opioids, play a role against the defense immune mechanism. They decrease the activities of the NKCs and CTLs, and their production. Fentanyl decreases the cytokines production, activity of phagocytes, and liberation of the antibodies.[4] IL-2, an activator of the NKCs, was not changed during sevo-fentanyl and propofol-ketorolac anesthesia.[13]

However, local anesthetics protégé the body from perioperative stress and hormone release. Consequently, they reduce the variations of cytokines, the elements for inflammation and the immune function. They also regulate the cellular microenvironments during surgery and play an important role in the progression of breast cancer.[14]

Lidocaine, acting as a blocker of the voltage gated sodium channels, promises a variety of additional effects. Lidocaine prevents cytoskeletal modification in breast carcinoma.[11] In two studies it was shown that lidocaine inhibits the proliferation, invasion, and migration of cancer cells.[15,16] In the last decades, the possibility of lidocaine to sensitize some chemotherapeutics and enhance apoptosis was added to the lidocaine profile.[17]

Lockwood H. showed that a bolus IV dose of 1 mg/kg lidocaine given prior to induction of anesthesia, followed by infusion of lidocaine during surgery and in PACU resulted in a significant peroperative reduction of opioid use and statistically significant lower postoperative VAS scores.[18] Furthermore, it was found that local anesthetics can annul the immunosuppressive effects of volatile anesthetics.[14]

The role of TNFα in dissemination of the tumor cells is still unknown. In one study, TNFα was referred to be a key factor in mediation and killing of the tumor cells. It inhibits the proliferation of tumor cells and induces tumor apoptosis.[19] Several authors studied the influence of combined anesthesia and local anesthetics on cytokines activities in breast tumors, with preliminary

positive experiences.[20-22] However, they emphasized that the effects of TNFα depended on the gene expression of the subtypes of receptors in different types of breast carcinoma. The *in vitro* research in this field is still ongoing.[15] Regarding our results, the increase of TNFα in groups with combined anesthesia (Groups LA and Group PECS), compared to standard GA (Group GA), may be understood as an effect of the used local anesthetics (lidocaine and bupivacaine) as an increased immune response.

The postoperative appearance of a decreased activity of the NKCs and their lower cytotoxicity in breast carcinoma surgery is connected to poor prognosis.[23] From the immune aspect, the most important issue is the preserved number of T-cells, primarily lymphocytes, whose function is prevention of tumor cell dissemination. Several findings confirm that local anesthetics and regional blocks optimize physiological functions and play a stress relief and defense role for the body.[5,7] Their results showed a postoperative significant increase in the number of WBC's and neutrophils and a small decrease of lymphocytes in patients anesthetized with combined anesthesia,[9] which was in accordance with the results of our study. These results suggest that local anesthetics are responsible for the variations in the WBC level. Radical mastectomy is an extensive surgical procedure: the breast with the surrounding tissues in the region is completely removed (pectoral muscles and nerves are preserved) and a huge resection of the lymph nodes in the axillas is done. Such extensive operative procedures are followed by an increase in WBC's.

Regional anesthetic techniques such as epidural anesthesia, paravertebral block, PECS I/II blocks, and the use of local anesthetics have several advantages such as opioid sparing effect, stable hemodynamics, and perioperative pain relief. Several studies confirmed the advantage of the use of the combined technique over GA.[24,25] Matsumoto and his team assessed the benefits of the use of PECS Blocks during mastectomy. They found that combined anesthesia GA with PECS I/II block reduced the postoperative pain scores, the need for opioids, postoperative sedation, and side effects. They also found an elevation of the IL6, suggesting that surgery modulates the immune system.[26]

Additionally, was found that the application of PECS I/II blocks in breast carcinoma surgery resulted in a significant hemodynamic stability compared to balanced general anesthesia, which was confirmed by several other authors also.[20]

In our research was also found that PECS I/II blocks offer lower VAS scores and better postoperative analgesia. The opioid use and postoperative complications were lower, and the recovery was enhanced.

When going one step further about the outcomes, when combined anesthesia was used, the study of Exadaktylos AK *et al*. in a relatively revolutionary manner confirmed that several tumor recurrences decreased.[20] Therefore, this encouraged us and other authors to analyze and investigate the follow-up outcomes.

5. LIMITATIONS

However, this study has several limitations. First, the study sample was small. Second, more relevant data regarding immune function and defense response to stress needs to be studied in the future research. This field of anesthesiology needs additional investigation with the aim of discovering the role of the immune system in spreading of the tumor cells, and dissemination of distant metastases.

6. CONCLUSION

The results obtained in this study have shown that the use of local anesthetics lidocaine and bupivacaine in form of combined anesthesia (GA with PECS I/II block or iv administration of lidocaine), enhanced the immune response during radical mastectomy due to breast carcinoma and are superior to the balanced GA. The benefits for the patients are hemodynamic stability, better analgesia during surgery, and less use of opioids which are the reason for unwanted effects on the immune function. Probably the main benefit of this anesthetic strategy is in conserving of the T-cells defending the immune function against the dissemination of the tumor cells. In our patients, a significant increase in the level of TNFα and a minimal decrease of the level of lymphocytes was observed. We can speculate that the slight change at the level of cytokines and leukocytes, better pain relief and stable hemodynamics augment because of the use of local anesthetics during mastectomy, is probably the most adequate type of anesthesia for patients with breast carcinoma. The main finding of this study is that the patients with PECS I/II block had significantly less postoperative complications compared to GA.

7. Future direction

This study was the preliminary research in the field of the effects of anesthetics on immune function. The authors are encouraged to continue their investigation in the course to discover the NKCs activities, and the T2/T1 ratio during the breast carcinoma surgery, to follow the three years survival rate of the patients and to develop a protocol for anesthesia of the patients for mastectomy.

8. Data availability

The numerical data generated during this research is available with the authors.

9. Conflict of interest

10. Acknowledgements

11. Authors' contribution

DLA, MVSH: design, acquisition of the data, drafting of the manuscript, final approval, agreement for all aspects of the work

AMK, MIKA: data analysis, critical revision, final approval, agreement

BKK: data interpretation, revision, final approval, agreement

AMK, VMD: acquisition of the data, drafting of the manuscript, final approval, agreement

MIJS, ADK: acquisition of the data, data interpretation, final approval, agreement

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