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Effects of Anesthesia Technics on Certain Cytokines for Patients Undergoing Surgery: A Clinical Diagnostic Study

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Keywords

Anesthesia technic, General Anesthesia, Spinal anesthesia, Cytokines, Immune system.

Abstract

Background: Change of circulating cytokines level were normally low and may be uncleared within 30 - 60 minutes during anesthesia. The concentration of most of cytokines increases at 2 - 4 hours after operation.

Materials and Methods: The prospective clinical diagnostic study was performed on 100 patients undergoing surgery. First blood samples were collected from the patients before induction and second samples were collected 6 hours after operation. Cytokine serum level tests were performed for all samples to diagnose the level of cytokine cell interleukin -6 (IL-6), interleukin -10 (IL-10), tumor necrosis factor -alpha (TNF-α) and interferon - gamma (INF-γ) pre- and post-operative.

Results: Most of patients operated with general anesthesia, The mean level of serum IL-6, IL-10 and TNF-α slightly increased after operation and significant differences were shown in patients whom under surgery for 2-3 hours ($p<0.05$) but significant changes of IFN-γ were higher ($p<0.001$). Significant elevations were seen after operation during general and mixed (spinal + general) anesthesia for IL-10 and TNF-α and IFN-γ. Post operative changes in mean serum level for IFN-γ was higher than the changes for IL-6, IL-10 and TNF-α and clearly significant were shown for patients who operated under GA or mix (SA+GA). Highly significant mean differences ratio (Before : After) anesthesia and surgery were shown for IL-10 during GA and SA+GA and INF-γ $p<0.001$.

Conclusion: General anesthesia significantly increases the serum level of IL-10, TNF-α and INF-γ rather than spinal anesthesia after operation. Therefore, spinal anesthesia and short-term operations not considerable and changes in the immune response for patients undergoing surgery

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1. Introduction

Anesthesia is the use of medicine to produce loss of sensation with or without loss of feeling and awareness by using medications which includes hypnosis, analgesia and muscle relaxation. This helps patients to afford surgery without the distress and pain. it was applied by three technique; general, regional, and local. General anesthesia suppresses central nervous system activity resulting in loss of consciousness and full sensation absence. Regarding regional anesthesia, spinal anesthesia is the commonest type was used during surgery(1, 2), is the insertion of local anesthetic solution into the cerebrospinal fluid (CSF) to perform loos of sensation from nerves suppling the area of the block.(3) Exposing to anesthesia may affect several functions of immune system during operation.(4) Most type of operations cause various metabolic, immunologic and hemodynamic syndrome.(5) Anesthesia affects the many types of cytokines that is one of the component of immune system which influence the inflammatory response postoperatively.(6)

Cytokines, including tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), and interleukin-10 (IL-10), are systemic inflammatory and anti-inflammatory immune responses. They are key modulators of inflammatory reactions and are closely related to the extent of tissue damage secondary to the activity of the immune system. Anti-inflammatory cytokines, such as IL-10, can inhibit the release of TNF-a and IL-6. As well as Interferon gamma (IFN-γ) is another cytokine that has ability to activate macrophage and simulate natural killer cells (NK) and neutrophils.(7)

Change of circulating cytokines level were normally low and may be uncleared within 30 - 60 minutes during operation. The concentration of most of cytokines increases significantly at 2 - 4 hours after operation. Under physiological conditions, cytokines act as immunomodulatory components within physiological conditions, which decrease potential damages or increase inflammatory reactions. On the other hand, systemic inflammatory response syndrome (SIRS) or immunosuppression began to start because of increasing cytokine level. During perioperative period distribution of central nervous system, cardiovascular system, lungs, liver, and kidneys may occur because of increasing level of cytokines. The concentration of cytokine level reached to peak at 24 hours after general anesthesia and it remains for 48-72 hours after operation at the same concentration.(7-10)

Also, pharmacological effects, neurological and hormonal pathways affected by anesthesia through cytokine response.(11) IFN-γ and IL-6 play important roles in hematopoiesis and immune response during stress and surgery.(12) The production of a variety of inflammatory cytokines, including IFN-γ and IL-6 suppressed by IL-10 and IL-4.(13, 14)

The observation of Immunosuppression peri and post anesthesia among patients undergoing surgery could be related to the activation autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Release of hormones such as

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catecholamines (norepinephrine and epinephrine), adrenocorticotropic hormone and cortisol in autonomic nervous system induced by surgical stress and HPA axis it is considered as an inhibitory factor on immune functions which raise cellular signaling lead to inhibit proinflammatory cytokine production.(15)

Moreover, surgical stress and drugs during surgery activate monocytes / macrophages and lymphocytes forms from cytokines such as IL-1, IL-6, and TNF-α were stimulated by HPA.(16) Therefore, the proinflammatory and anti-inflammatory cytokines as well as neuroendocrine system cooperatively have suppressive effects peri and post operatively on the immune system. Thus, the goal of this study is to indicate the effects of anesthesia and their techniques on certain inflammatory cytokine among patients undergoing surgery.

The aim of the study is to assess and compare the level of certain serum cytokines in patients who exposed to different anesthesia technics pre and post operatively.

2. Materials and Methods

Prospective clinical diagnostic study was conducted on 100 surgical ill patients. The present study was approved by College of Health and Medical Technology scientific ethical approval committee (ID: CH 00085). Patients consent and permission was taken from each patient. All the patients were healthy with normal cytokines level we studied preoperatively.

The hospitals from which we collected our data includes Sulaimani Teaching and Shar Teaching Hospital (General surgery department), from November 2021 to March 2022.

Random selection of 100 patients were studied, the ages were from 5 to 80 years old. Patients were randomly assigned in to spinal, general and combination of spinal with general anesthesia. Patients who undergo general anesthesia were administered with intravenous Propofol (2-3mg/kg) or Pentothal (2-3mg/kg) for induction with Fentanyl (0.5-2µg/kg) and or Ketamine (0.1-0.3mg/kg) as analgesics. After induction Rocuronium (0.6-1.2mg/kg) or Atracurium (0.5mg/kg) were given to patients as a muscle relaxant agent with Oxygen, 50% Nitrous Oxide and 0.8% isoflurane.

For patients under spinal anesthesia 10–15mg bupivacaine and 15mcg of Fentanyl were administered intrathecally.

As well as, other patient who undergo combined with spinal and general anesthesia at the first for spinal anesthesia (SA) they were received sedation [Midazolam (0.05-0.08)] after became with GA they were given all medications of GA ether because of failed spinal anesthesia or prolongation of operation.

The first samples of blood were taken on the day of surgery 30 minute before the induction of anesthesia; the second samples blood were taken after 6 hours of surgery for Cytokines detection. 5ml of blood samples from all tested patients were drawn via an indwelling catheter inserted into a forearm vein from median cubital, cephalic and basilic veins putted to a jell tube. After 5 minutes the sample putted in the centrifuge for 5 min/rpm to separate serum from blood. After centrifugation the samples were putted in

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to the freezer under -25 C°. After one day freezing, we used incubator to prepare the serum for analyzing to obtain cytokines serum level (IL-6, IL-10, TNF-α and IFN-γ) by using ELISA kit according to the manufacture RayBiotech and the final reading was by ELISA reader (BioTek 800 TS microplate reader machine).

Inclusion criteria contains all the patients were healthy with normal white blood cell counts preoperatively.

Exclusion criteria were patients under 5 years old and who had abnormal white blood cell count were excluded.

Statistical analysis: Data management and statistical analysis were done by using Statistical Package for the Social Sciences (SPSS) version 22. Categorical data was compared by using Chi-square test (χ^2). (ANOVA) test and independent sample *t*-test used to perform relations between the mean and variables. P-value of <0.05 was looked as statistically significant between the variables.

3. Results

A total of (100) patients, were studied, of whom 36 (36%) patients were males and 64 (64%) were females. Majority of cases (55%) age were 20-40 years old. According to the types of anesthesia, in both female and male majority of them were under GA 28% and 26% respectively. Also, most of patients age were between 20-40 years old under GA 23%. (Table 1)

Table 1. Distributions of demographic data according to types of anesthesia. n=100

	Variable	%	SA	GA	SA+GA
Gender	Female	64	23	28	13
	Male	36	4	26	6
Age groups	<10	8	0	8	0
	10-20	8	0	7	1
	20-40	55	15	23	17
	>40	29	6	15	8

SA: spinal anesthesia, GA: general anesthesia, SA+GA: combined spinal and general anesthesia

The result of table 2 showed that most of the patient's duration of operation were between 1-2 hours 48 (48%). The mean level of serum IL-6, IL-10 and TNF-α slightly increased after operation and significant differences were shown in patients whom under surgery for 2-3 hours. But changes of mean serum level IFN-γ significantly were seen in higher level than other cytokines for in all duration of surgery. (Table 2)

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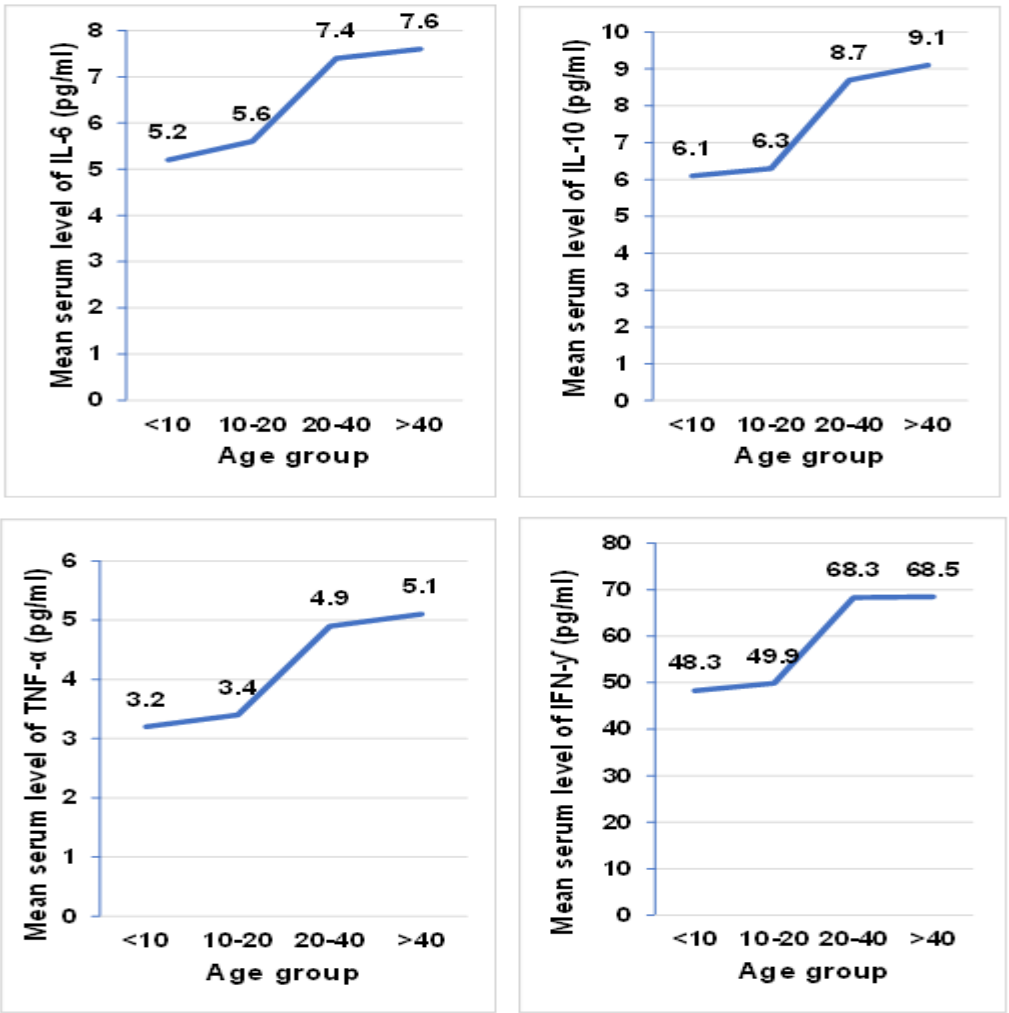
Table 2. Distribution of mean cytokine counts before and after operation with duration of operations. n=100

Duration of operation (N)	IL-6		IL-10		TNF-α		IFN-γ	
	Before	After	Before	After	Before	After	Before	After
< 1 hour (30)	6.5	7.1	5.5	6.3	3.2	4.1	16.1	40.2*
1-2 hours (48)	6.3	7.5	5.4	7.3	3.0	4.8	16.4	50.3*
2-3 hours (17)	6.2	8.9*	5.1	8.1*	3.5	5.9	16.3	60.9*
> 4 hours (5)	6.6	14.3	5.3	10.8	3.8	9.1	17.6	70.6*

SA: spinal anesthesia, GA: general anesthesia, SA+GA: combined spinal and general anesthesia, IL-6: interleukin-6, IL-10: interleukin-10, TNF-α: tumor necrosis factor alpha, INF-γ: interferon gamma.
* Significant differences considered p<0.05

Figure 1. Mean cytokines serum level according to the age groups. IL-6: interleukin-6, IL-10: interleukin-10, TNF-α: tumor necrosis factor alpha, INF-γ: interferon gamma.



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In general, the mean serum level increased with increasing ages for patients' exposure to anesthesia and surgery and reached to peak for patients more than 40 years old. (Figure1)

Table 3 showed that significantly the mean serum level was increased post operation for IL-6, IL-10 and IFN-γ in patients under GA, also for IL-6, IL-10, TNF-α and IFN-γ increase of serum level were significantly after operation for SA+GA anesthesia $p < 0.005$. But for all cytokines clearing SA there was no significant changes postoperatively. (Table 3)

Table 3. Comparison of mean cytokines counts pre and post operation with type of anesthesia. n=100

Type of operation	Cytokines	Pre-operation	Post-operation	P-value
SA	IL-6	7.8	8.1	0.23
	IL-10	5.3	6.1	0.35
	TNF-α	3.4	3.5	0.42
	IFN-γ	16.5	16.8	0.54
GA	IL-6	8.3	13.6	<0.001
	IL-10	5.6	7.6	0.03
	TNF-α	3.3	4.8	0.12
	IFN-γ	16.9	55.3	<0.001
SA+GA	IL-6	8.6	14.7	0.005
	IL-10	5.8	9.1	0.02
	TNF-α	3.5	6.7	0.03
	IFN-γ	16.1	64.2	<0.001

SA: spinal anesthesia, GA: general anesthesia, IL-6: interleukin-6, IL-10: interleukin-10, TNF-α: tumor necrosis factor alpha, INF-γ: interferon gamma.

In figure 2 the highly significant mean differences ratio (Before : After) anesthesia and surgery were shown for IL-10 during GA and SA+GA (0.0 : 5.3 and 0.0 : 6.1) and INF-γ (0.0 : 38.4 and 0.0 : 48.1) $p<0.001$. For all types of cytokines, the mean differences ratio not significant in patients under SA. (Figure 2)

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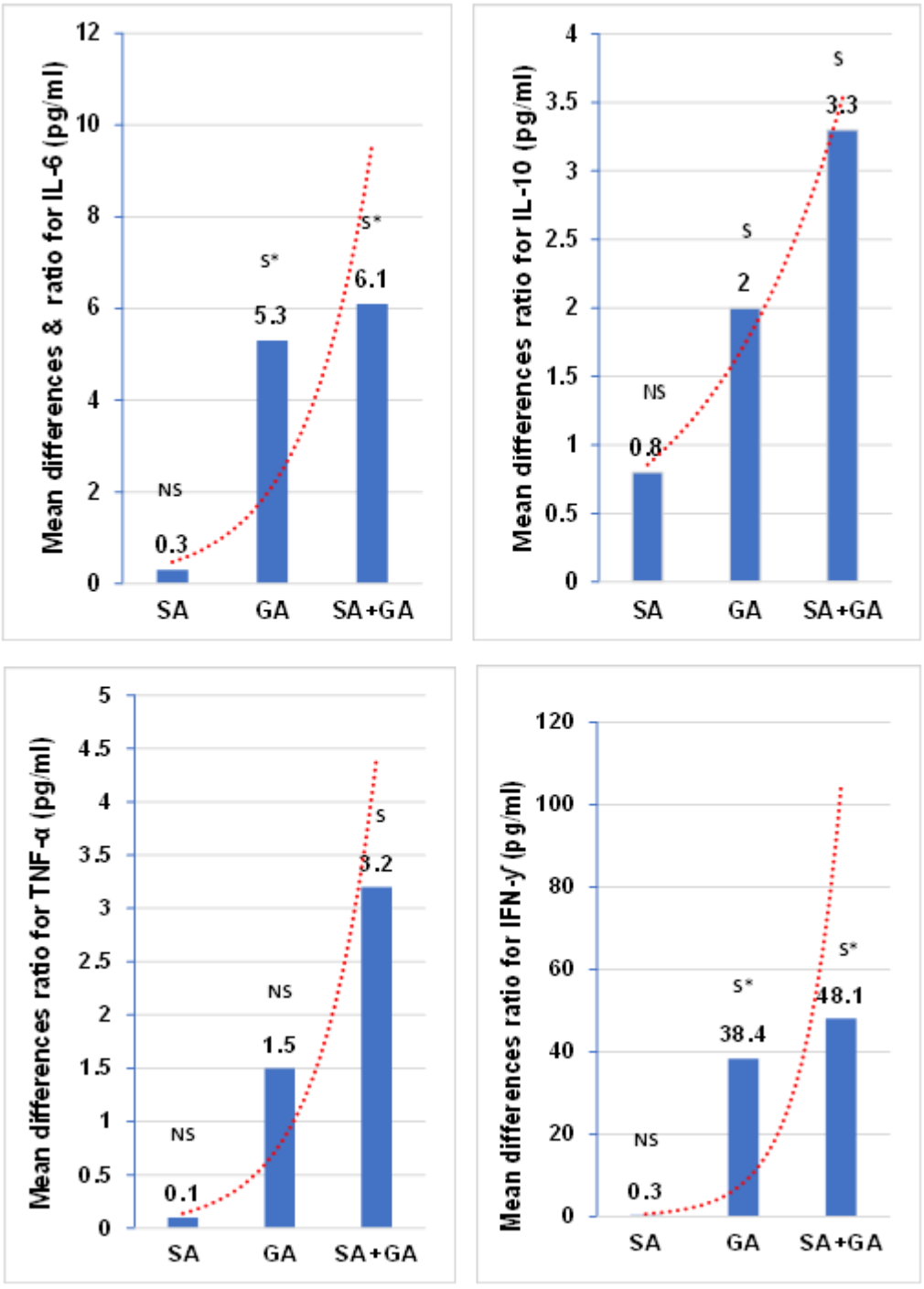

Figure 2. Comparison of cytokines mean difference serum level ratio before to after operations. SA: spinal anesthesia, GA: general anesthesia, SA+GA: combined spinal and general anesthesia, IL-6: interleukin-6, IL-10: interleukin-10, TNF-α: tumor necrosis factor alpha, INF-γ: interferon gamma, S: Significant differences considered $p<0.05$, S*: Highly Significant differences considered $p<0.001$.

Figure 3 showed that the change of level serum cytokines gradually increased post

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operation for patients under GA and SA+GA, there was no or slightly changes in patients under SA. (Figure 3)

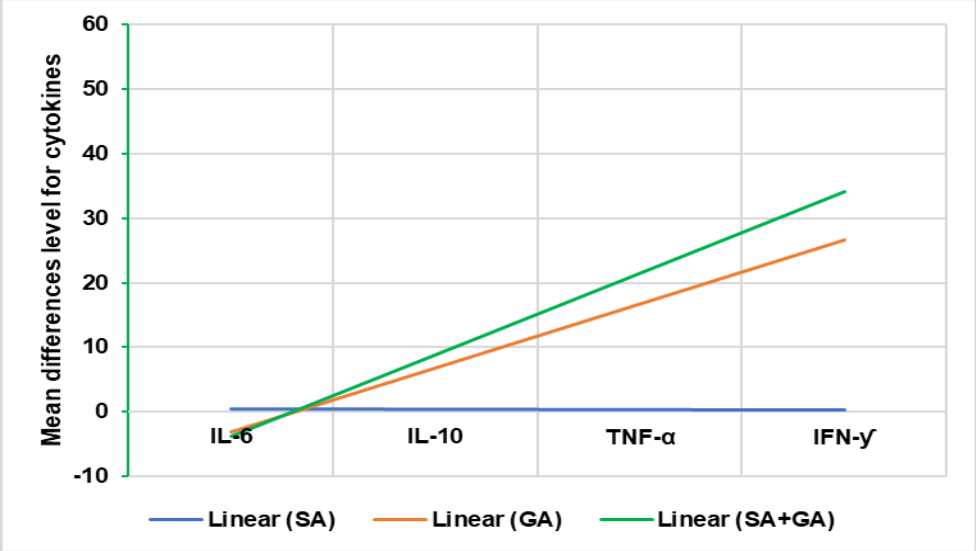

Figure 3. Cytokine mean differences levels regulation according types of anesthesia. GA: general anesthesia, SA+GA: combined spinal and general anesthesia, IL-6: interleukin-6, IL-10: interleukin-10, TNF-α: tumor necrosis factor alpha, INF-γ: interferon gamma.

4. Discussion

The current study was conducted to find effects of anesthesia and compare the effects of anesthesia technic on serum level of some cytokines such as (IL-6, IL-10, TNF-α and INF-γ) for patient undergoing surgery in different age groups and different types of surgery. Our result demonstrated that general anesthesia is the most anesthesia technic was used for patients during surgery. This could be due to nature of patient management requirement according to the types of surgery. Also, patients age groups 20-40 years old were the most groups exposed to surgery than other groups. On the other hand, GA is a prominent type of anesthesia in our groups rather than others. This may be due to lymphoproliferation younger age has more ability to produce and recover immunomodulatory cells especially, cytokines.(17) So, for instance that is a good indicator to decide and was identical to previous studies demonstrated that anesthetics administration may affect levels of genes expression in relation to inflammatory cytokines and chemokines.(18-20)

Regarding duration or time of operation, we found that the level of serum cytokines increased with prolongation of operation. Moreover, the postoperative mean serum concentration of IFN-γ for all times, as well as elevation of mean serum level of IL-6 and IL-10 for patients underwent operations for 2 to 3 hours after operation were significantly higher than other duration of surgeries. Prolong exposure to surgical stress and anesthetic agents during operation leads to exert through activation of numerous stimuli including release some cytokines; the most potent stimulus lipopolysaccharide or their component of endotoxin which induce cytokine production like IL-1, IL-6 and IL-10.(10) On the contrary, period of a major surgery

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has a significant immune suppression and some cytokine depletion that results from interaction of many factors such as dose of analgesics used perioperatively to control pain.(21)

The present study demonstrated that the mean serum level of all types of cytokines we studied not significant in patients with SA except IL-10. On the other hand, increasing of serum level were shown in patients with GA and SA+GA. However, the change between those two groups is significant ($p<0.05$), but for IFN- the significant was higher in patient who operated by both SA and GA ($p<0.001$). The season may be that the level of IL-6, TNF-α and IFN-γ usually rises hours after the surgery especially patients operated by GA. A M mahdy et al. reported that level of IL-6 increased after GA surgery rather than IL-10 because IL-6 is a multifunctional protein which early released among operation which mediate the release of acute-phase protein.(22)

In the present study significant reactions were found in patients during GA and SA+GA postoperatively for all serum level cytokines except TNF-α during GA, however the mean serum level increased. In spite of this no significant relation between pre and post operative serum level cytokines for patients during SA. These finding are in consistent with those of previous studies which demonstrated that surgical trauma by GA plays important roles to release inflammatory cytokines than other types of anesthesia postoperatively.(23, 24) Also, Preoperative levels being similar, the cytokine levels increased at 2 hours and peaked at 4 hours [Contradictory, another study has reposted that the effects of regional anesthesia including SA on serum level of plasma epinephrine/cortisol were shown to be significantly decreased but IFN-γ and TNF-β increased depending on the increasing T-helper cells and lymphocytes post operation than the other types of anesthesia.(25) According to the previous finding by Zhang J et al. during general anesthesia anesthetics, pain, as well as surgical stress intraoperatively, leads to increase adrenergic nerve activity and plasma concentration of catecholamine by an autonomic response.(26)

Regarding mean differences ratio before to after anesthesia highly significant mean deference ratios were seen for IL-6 and IFN-γ during GA and SA+GA, however slightly significant was shown for IL-10 during GA and SA+GA. But there were no significant mean difference ratios during SA. In addition, TNF-α mean difference ratios predominately stable and there were no significant changes during types of surgery. This indicates that human clinical studies more complex especially in investigations of patients' immune system cytokines involving interleukins, tumor necrosis factors and interferons which affected by anesthetic agents, anesthesia technics that interact with other factors such as endogenous patient's characteristics and exogenous factors.(26)

Finally, we suggested that the mean differences level of IL-10, TNF-α and IFN-γ gradually increased according to types of surgery, while the mean differences level of IL-6 was stable during all types of anesthesia. Previous studies have confirmed that serum level of cytokines regulated and more activated by

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inflammatory response during anesthesia induction directly affecting the immune system or activating the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system lead to production of interleukins and TNF-α.(10, 27) On the other hand, suspected studies revealed that general anesthesia accompanied by surgical stress is considered to suppress immunity is related to the neuroendocrine stress induced release of epinephrine and norepinephrine hormone as well as cortisol via nervous system mediates inhibitory effects on immune system functions and cellular signaling lead to inhibit the proinflammatory cytokines as well as monocyte/macrophage and lymphocytes.(15, 28)

Interestingly, increasing of the serum level of cytokines after anesthesia especially GA is necessary to human begin tissue repair and inflammation reduction, because anesthesia surgical split and tissue damage shift the balance of serum cytokines across proinflammatory factors leads to increase interleukins and TNF-α.(23) However, inflammatory response induced by immune cells may increase the emerging post-surgical complications impaired wound healing systemic inflammatory response and severe hemodynamic disorder, and multiple organ failure.(29) It seems that spinal anesthesia tended to induce lower inflammatory response.(20)

An impairment and immunosuppression during perioperative and postoperative periods have substantial clinical implications because the risk of emerging postoperative infection and sepsis were involved. Since postoperative hospital staging and evaluating are the most beneficial status, we recommended in order to give appropriate care for patients. As well as appropriate anesthesia leads to decrease perioperative and postoperative complications. For this reason, anesthesiologist should be aware during operation of the disadvantages of anesthetics and anesthesia technic because research on human various factors interfere for example gender, anesthetic drugs duration of operation surgical types and surgical stimulus as well as patients' health conditions. Clearly, future studies necessary to detect and follow up immune function cytokines for longer period of times.

We have some limitations in our study we stopped our evaluations at 6 hours after surgery as well as the number of cytokines is more, but we choose four of them. The strength of our research is that we investigated effects of anesthesia on immune cytokines responses before and after anesthesia administrations in different cells.

5. Conclusion

According to the result of our study anesthetic techniques such as general anesthesia alone and spinal together with general anesthesia affect the inflammatory response and could be associated with immune functions through their effects on different cytokines postoperatively. As well as prolong duration of operation was another indicator which increase serum level cytokines for patients undergoing surgery. At the end of this study, we found that spinal anesthesia has less effects on the immune response cytokines and it

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could be the safest techniques during surgery.

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