Original Article

# Effect of Spinal and General Anesthesia on Serum Cytokine Levels Following Cesarean Section in Preeclampsia

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## Abstract

*Background:* The purpose of this study is to investigate the impact of different anesthetic techniques on the release of cytokines interleukin IL-6, IL-10 and tumor necrosis factor (TNF)-α in preeclampsia patients who undergo cesarean section.

**Materials and Methods:** In the study 40 patients were enrolled with preeclampsia undergoing cesarean section, allocated into two equal groups to receive either general anesthesia (n = 20) or spinal anesthesia (n = 20). Non-invasive hemodynamic monitoring was used. Serum levels of IL-6, IL-10 and TNF-α were measured before and at the end of surgery.

**Results:** There was no significant rise in serum levels of TNF-α in general anesthesia while IL-6 and IL-10 serum levels increased significantly. Also, compared with patients anaesthetized with general anesthesia patients who received regional anesthesia notably had lower levels of IL-6 and IL-10 after surgery ($p < 0.05$).

**Conclusion:** Spinal anesthesia causes significant difference in post-operation IL-6 and IL-10 serum levels in preeclampsia patients undergoing cesarean section. Nevertheless, neither general nor spinal anesthesia made such effect on serum level of TNF-α. Further studies with higher sample size and comparing preeclamptic patients to healthy mothers undergoing cesarean section are required.

**Keywords:** Spinal Anesthesia, Preeclampsia, General anesthesia, Interleukin-10, Interleukin-6, TNF-α, Cesarean Section

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## Introduction

Preeclampsia (PE) is a syndrome that affects 2% to 8% of human pregnancies and constitutes a major cause of maternal and perinatal morbidity and mortality (1). It is a systemic disease characterized by an inflammatory response and endothelial disorder, and is clinically identified by a combination of hypertension and proteinuria, presenting after 20 weeks of gestation in a previously normotensive pregnant woman (2, 3). Previous studies suggested that an abnormality in immunologic balance has been implicated in the pathology of preeclampsia (4). The ischemia and hypoxia resulting from the inappropriate trophoblast invasion lead to an increased production of pro-inflammatory cytokines in the placenta (5).

The roles of the various cytokines in the pathology of preeclampsia have been studied by several authors, with conflicting reports on the serum concentrations of interleukins in preeclampsia (6-8). These studies showed high levels of interleukin (IL)-1, IL-6 and tumor necrosis factor alpha (TNF-α), IL-2 and interferon gamma (IFN-γ), are overexpressed and secreted in placentas of preeclamptic women likely due to hypoxia-reoxygenation caused by intermittent placental perfusion (9). All these inflammatory cytokines seem to have deleterious effects on pregnancy development (10-12).

Prompt control of hypertension, fluid restriction, seizure prophylaxis in high-risk groups, and expedited delivery in the presence of severe maternal disease features or fetal compromise, are the core principles during preeclampsia management (13, 14).

As with other surgical procedures cesarean section provokes further increases in serum cytokine levels with consequences on host immunomodulation and recovery of the parturient (15).

The establishment of safe regional anesthesia (RA) for labor and caesarean delivery in preeclampsia is one of the most important developments in the past 25 years in obstetric anesthesia. Spinal anesthesia offers advantages in preeclampsia in terms of hypertension control and simplicity of airway management (16, 17). The advantages of regional anesthesia over general anesthesia are documented in many studies (e.g., inhibition of metabolic and hormonal responses to stress, reducing the incidence of post-operative pain, speeding peristalsis after abdominal operations, reducing the incidence of deep vein thrombosis, and shorter hospital stay). Unfortunately, it cannot always be applied. The potential disadvantage of regional anesthesia is its limited duration (18).

The indications for general anesthesia (GA) for caesarean section in preeclamptic women with preserved ejection fraction are eclampsia with altered mentation, coagulopathy, and thrombocytopenia. Although new evidence is sparse, in hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome most anesthesiologists adhere to an early report, which showed that thromboelastographic maximum amplitude, decreased once platelet numbers dropped below 75x109.L-1. Abruptio placentae without maternal hemodynamic compromise or cardiotocography abnormality are not a contraindication to RA (19). General anesthesia introduces problems of difficult tracheal intubation, and the hypertensive response. Therefore, ideal modern management for preeclamptics is early establishment of epidural analgesia in labor and spinal anesthesia for caesarean delivery in cases in whom an epidural catheter has not been inserted. However, many units around the world still provide routine general anesthesia (20-23). The advantages of general anesthesia are its simple and easy method of application, rapid sedation of the patient, and increased comfort of surgeons and anesthesiologists when the surgery has to last longer. The disadvantages of general anesthesia are airway management during intubation, challenges in controlling hypertension caused by intubation and extubation, and postoperative adverse effects (e.g. nausea, vomiting, and pain) (24). Although several studies have been conducted on the effects of different anesthetic methods on activity of inflammatory cells and serum levels of interleukins, but so far, no studies have been established to compare both general and regional anesthesia on the interleukin levels in pregnant women with preeclampsia. The aim of the study was to determine the significance of spinal anesthesia in suppressing levels of immune-associated compounds found in the plasma of patients suffering from preeclampsia comparing to general anesthesia.

# Methods

### Patients

The study included 48 patients, 24 in the general anesthesia group and 24 in the spinal anesthesia group (Fig. 1). In the general anesthesia group (group I), four patients were excluded due to technical issues in sample collecting. In the spinal anesthesia group (group II), two patients were excluded due to conversion from spinal anesthesia to general anesthesia during surgery, and another two patients were dismissed from the study due to technical laboratory problems. A total of 40 preeclampsia patients undergoing Cesarean Section (C/S), with an American Society of Anesthesiologists (ASA) physical status of I or II were included in the current study. The Ethics Committee of Shahid Beheshti University of Medical Sciences approved the study protocol and all the patients provided written informed consent prior to inclusion. The exclusion criteria included eclampsia, coagulation disorders of any type, history of anti-phospholipid syndrome and history of any allergy to the drugs used in the study.

The lead physician independently conducted patient assessments for inclusion based on the patient's medical history. Subsequently, the patients were randomly assigned in two groups (n=20 per group) using a computer-generated table of random numbers. The lead physician was also primarily responsible for drug preparation in order to ensure consistency of drug administration throughout the study.

**Types of anesthesia**

Group I received general anesthesia and group II received spinal anesthesia. During the operation, patients were continuously monitored using a combination of electrocardiography, noninvasive blood pressure recordings and pulse oximetry techniques.

Group I patients received intravenous anesthesia induction with 4-6 mg/kg Thiopental and 1-1.5 mg/kg Succinylcholine following 0.8% Isoflurane for anesthesia maintenance. Spinal anesthesia performed by injection of single dose of 2.8 cc Bupivacaine 0.5% at the L3–L4 interspace using a 25-gauge Quincke point needle in groups II.

**Clinical Diagnosis of PE**

Preeclampsia was diagnosed by new-onset blood pressure ≥140/90 mmHg and significant proteinuria (urinary total protein/creatinine ratio >30 or +1 on urine dipstick). All cases were diagnosed after 34 weeks' gestation (late-onset PE).

**Blood samples**

Peripheral blood samples for the detection of IL-6, IL-10 and TNF-α levels were collected prior to the induction of anesthesia (T0), and postoperatively, 30 minutes after transferring the patient to recovery room and before discharge (T1). The sampled blood was collected into EDTA tubes and centrifuged at 2000 rpm for 3 min at 4˚C immediately after sampling. Thereafter, the plasma samples were stored at -20˚C until all the samples were collected. The samples with the temperature of 0°C were transferred to laboratory at Department of Immunology to assess with an ELISA assay (Mabtech, Nacka Strand, Sweden).

**Detection of plasma IL-6, IL-10 and TNF-α levels**

Interleukin-6, IL-10 and TNF-α levels in the plasma were assessed using commercial quantitative ELISA assay kits (Mabtech, Nacka Strand, Sweden) according to the manufacturer's instructions. Standards were prepared and the appropriate volume of sample or standard was added to a 96-well polystyrene microtiter plate pre-coated with monoclonal antibodies either to the appropriate cytokine or to the related antigen. All samples and standards were run in duplicate and the plates were incubated for the recommended time. Each well was subsequently aspirated and the plates were washed with the provided buffered surfactant. An enzyme-linked polyclonal antibody against the cytokine was then added and the plates were incubated a second time prior to final washing. After addition of the substrate solution to each well, the optical density was read at the appropriate wavelength for each assay period. All the values were reported as picograms/milliliter. Interleukins were measured (with a sensitivity of 0.5 to 1 micrograms/liter. Cross-reactivity with other factors was considered negligible in all the cytokine assays.

**Statistical analysis**

All quantitative data are expressed as mean ± SD. Patients characteristics such as age and sera interleukin levels were calculated by student t-test. Categorical data were described as absolute frequencies and analyzed using the Pearson's $\chi 2$ and Fisher's exact tests. P<0.05 was considered to indicate a statistically significant difference. All the data were analyzed using the SPSS statistical software, version 22.0 (SPSS Inc., Chicago, IL, USA).

# Results

Data from 40 patients, 20 in the general anesthesia group and 20 in the spinal anesthesia group, were included in the final analysis. None of the patients

**Table 1:** Baseline demographics and surgical procedure

| | I | II | P value |
|---|---|---|---|
| Age | 32.63±1.4 | 32.73±4.3 | 0.94 |
| Mean number of previous pregnancies | 1.75±1.0 | 2.10±1.1 | 0.29 |
| Number of previous abortion | 2 (10%) | 4 (20%) | 0.50 |

The results are expressed as mean ± SD or number of patients

The differences between groups were not significant (p > 0.05)

**Table 2:** Prevalence of intraoperative methyldopa, labetalol and magnesium sulfate

| | I (%) N | II (%) N | P value |
|---|---|---|---|
| Methyldopa | (65%) 13 | (35%) 7 | 0.113 |
| Labetalol | (70%) 14 | (40%) 8 | 0.111 |
| Magnesium sulfate | (80%) 16 | (65%) 13 | 0.480 |

The differences between groups were not significant (p > 0.05)

**Table 3:** Comparison of IL-6, IL-10 and TNF-α serum levels before and after surgery in each group.

| | T0 | | T1 | | P value |
|---|---|---|---|---|---|
| | I | II | I | II | |
| IL-6 (pg/mL) | 2.81±1.5 | 2.52±0.9 | 10.44±7.4 | 5.80±4.2 | 0.04* |
| IL-10 (pg/mL) | 3.72±3.5 | 5.44±4.1 | 8.14±6.3 | 5.41±4.4 | 0.02* |
| TNF-α (pg/mL) | 3.59±0.3 | 3.25±0.2 | 3.69±0.3 | 3.67±0.6 | >0.05 |

The results are expressed as mean ± SD or number of patients, T0=before surgery, T1=after surgery.

*between two groups in T1

had signs of preoperative infection. All patients underwent C/S because of preeclampsia. No significant differences were found between the groups regarding their demographics (Table 1).

Neither were there any significant differences in the use of intraoperative methyldopa, labetalol and magnesium sulfate that could have influenced the inflammatory response (Table 2). Patients in spinal

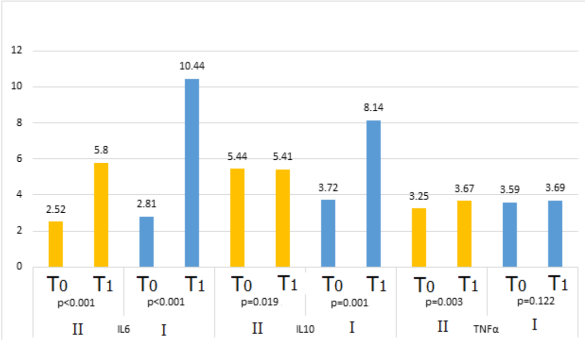


**Figure 1.** Comparison of changes in IL-6, IL-10 and TNF-α levels before surgery and 30 min after arrival in the recovery room in each group. Values are in pg/mL
I=general anesthesia, II= spinal anesthesia
T0=before surgery, T1=after surgery
P-value<0.05 was considered statically significant

anesthesia group had significant lower IL-6 serum level in comparison with general anesthesia in T1 (p=0.04) (Table 3).

## Discussion

We hypothesized spinal analgesia in compare with general anesthesia could dampen release of inflammatory cytokines response to C/S in pregnant women with PE. Results of this study demonstrated a statistically significant increase in post-operation levels of the inflammatory cytokines (IL-6, IL-10 and TNF-α). In addition, there were significantly higher serum levels of the IL-6 and IL-10, in the pregnant women with preeclampsia in general anesthesia group compared with those in spinal anesthesia after C/S.

Naturally, there is a balance between the release of pro and anti-inflammatory cytokines. But inflammatory reactions induced by immune cells can exacerbate the pro-inflammatory response and increase the incidence of postoperative complications, including infections, delayed surgical wound healing, cognitive impairment and even progression of malignancies, systemic inflammatory response syndrome (SIRS), and lead to severe hemodynamic disorders and multiple organ failure (25-28).

There is a consensus about the role of surgical incision and any tissue damage in increasing the serum levels of pre-inflammatory cytokines such as interleukin-1, interleukin-6 and TNFα, in turn enhancing the activity of the hypothalamic-pituitary-adrenal axis and the secretion of glucocorticoids (29, 30)

On the other hand, recent studies showed that although normal pregnancy is associated with a controlled inflammatory process, but pathological conditions like PE associated with higher levels of IL-1, IL-6, IL-10 and tumor necrosis factor alpha (TNF-α), as well as IL-2 and interferon gamma (IFN-γ), in plasma and amniotic fluid of PE women. All these inflammatory cytokines seem to have deleterious effects on pregnancy development (4, 31, 32).

Taylor *et al*., examined IL-6 levels during the second trimester and found that elevated levels of this cytokine predicted term PE (33). In other case–control studies during the third trimesters, researchers reported a significant increase in levels of IL-6 in pregnancies complicated by PE compared to normal pregnancies (34-38). In the same way, other researchers showed significant increased levels of IL-10 and TNF-α in pregnancies with PE when compared to normal pregnancies in the third trimester (38-42).

It is also demonstrated that anesthetic agents, anesthesia type, and anesthesia duration might affect the neuro-immuno-endocrine systems during surgery and influence this response (43-46).

The effects of different anesthetic techniques on perioperative changes in cytokine serum levels have been studied in surgical patients. When compared to general anesthesia alone, general anesthesia combined with continuous epidural anesthesia has not been shown to attenuate increases in IL-6 levels following radical esophagostomy, while TNF-α levels did not change in either group (47).

Circulating IL-6 levels have been found to increase in patients undergoing total hip replacement under both general and spinal anesthesia, while no significant changes were observed in TNF-α levels in either group (48). Similarly, 24 hours after hemorrhoidectomy under general or spinal anesthesia IL-6 increased with both anesthetic techniques while TNF-α levels remained the same (49).

In another study, IL-6 levels have been shown not to differ between patients undergoing abdominal hysterectomy under general or combined epidural and general anesthesia (50).

In liver cancer resection surgery, serum level of IL-10 of patients who underwent general anesthesia combined with epidural block showed a non-significant decrease immediately after surgery, but increased 24 hours after surgery, and the increase was greater than that of the general anesthesia group (51). Sun *et al*., reported significant differences in IL- 6, and IL- 10 serum levels between the combined intravenous and inhalation anesthesia and the combined general and epidural anesthesia groups 72 hours after surgery (52).

Different general anesthesia techniques for hysterectomy have been shown to influence cytokine levels, with Propofol and Alfentanil associated with lower serum IL-6 levels than isoflurane anesthesia (53). However, it has been reported, again with abdominal hysterectomy, that IL-6 levels increased in a similar fashion after fentanyl administration (54). In patients undergoing pancreatoduodenectomy both IL-6 and TNF-α levels increased, an effect that was not influenced by supplemental epidural analgesia (55). However, all these studies included only small numbers of patients and may therefore have been underpowered.

Karadeniz *et al*., showed that, there was no statistically significant difference in serum TNF-α levels between groups general anesthesia and general/epidural anesthesia at preoperative and postoperative 1$^{st}$ hour and 24$^{th}$ hour after radical cystectomy (56). In another study in degenerative disease of the spine 30 min after incision we observed significant larger concentration of IL-6 in general anesthesia group compared to group of spinal anesthesia (57).

In cesarean section, Jongh *et al*., measured IL-6, 12 and 24 hours after C/S under either epidural or general anesthesia. In their study, IL-6 levels peaked at 12 hours and remained increased for 24 hours postoperatively with both anesthetic techniques (58). Therefore, it seems that the cytokine response to cesarean section is not influenced by anesthetic technique and is comparable with the changes after elective general surgical procedures. In the same way, Dermitzaki *et al*., also showed significant increase in IL-6 serum level and no TNF-α in elective C/S. In addition, both groups did not differ in IL-6 or TNF-α serum concentrations at any time point (59).

Blood samples in our study were collected pre-operatively and 30 min after transferring the patient to recovery room after surgery. This could be seen as a limitation to our study. Reikeras *et al*., reported that IL-6 serum levels peak 6 to 24 hours after surgical procedures (60). Current literature suggests that, after elective surgical procedures, IL-6 remains elevated for 48 to 72 hours (55, 61).

Our results are consistent with those studies, demonstrating a postoperative increase in IL-6 and IL-10 levels, which is influenced by spinal anesthesia, while TNF-α levels were not significantly different between the groups. However, in spinal anesthesia group, there was significant increase in TNF-α while it was not significant in general anesthesia. The results of this study can be substantiated that the level of serum cytokines during surgery and the effect of different anesthetic methods on them can be influenced by the underlying diseases.

The delay of IL-6 increase postoperatively may be related to the synthesis of IL-6 mRNA, which is responsible for its production (62). Lee et al., showed that serum levels peak is 2 h for IL-10 and 2 to 24 hours for TNF-α after surgical procedures (63). Although the results of this study were in line with the results of other studies, it seems that increasing the number of blood samples taken over a longer period can give more conclusive outcomes, regarding the effect of using different anesthetic methods on the level of inflammatory cytokines in the patients. Further studies with higher sample size and also comparing patients with preeclampsia with healthy mothers of cesarean section are required to provide more information about the benefits of using different anesthetic methods on serum levels of inflammatory cytokines in preeclampsia.

# Conclusion

Results of the present study demonstrate that spinal anesthesia causes significant difference in post-operation IL-6 and IL-10 serum levels in PE women undergoing cesarean section. But neither general nor spinal anesthesia made such effect on serum levels of TNF-α.

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# Conflicts of Interest

The authors declare that they have no conflict of interest.

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