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The effect of different anesthesia applications on serum Pentraxin-3 levels: a randomized prospective study

Hatice Betul Altinisik[1]*, Fatma Beyazit[2], Hakan Turkon[3]

1 Dept of Anesthesiology and Reanimation, Canakkale Onsekiz Mart University, Medicine Faculty, Canakkale, TR
2 Dept of Obstetric and Gynecology, Canakkale Onsekiz Mart University, Medicine Faculty, Canakkale, TR
3 Dept of Medical Biochemistry, Meddem Hospital, Isparta, TR

*** Corresponding Author:** Hatice Betul Altinisik **E-mail:** drhaticebetul@gmail.com

ABSTRACT

Objective: Pentraxin-3 (PTX3) is a biomarker shown to correlate with the severity of infections. It is a good indicator of mortality and is useful in monitoring treatment success. However, there is inadequate information about the factors affecting PTX3 levels. This study aimed to investigate the effects of different anaesthesia types on serum PTX3 levels.

Materials/Patients and Methods: Serum PTX3 levels were obtained from patients who were under general anaesthesia (GA) and spinal anaesthesia (SA) for a caesarean section (C-section). Blood Samples were collected preoperatively at 6 h and 24 h postoperatively. Biomarkers such as C-reactive protein, white blood cells, neutrophils and lymphocytes were also assessed as biomarkers.

Results: No difference was found in the preoperative serum PTX3 levels among the participants ($p > 0.05$). A significant increase was observed when the preoperative PTX3 levels (0.16 ng/mL) were compared with the postoperative levels at 6 h (0.25 ng/mL) and 24 h (0.54 ng/mL) in the GA group. No significant change was found in the PTX3 levels at 0–6–24 h measurements in the SA group. Nevertheless, the GA group was found to be significantly higher than the SA group at 6 h and 24 h postoperatively ($p < 0.05$). Additionally, No correlation was observed between PTX3 levels and other biomarkers.

Conclusions: This study showed that when coupled with C-section, GA increased the PTX3 levels postoperatively compared with the PTX3 levels during the preoperative period. No significant change was observed with SA. The PTX-3 levels should be considered to increase in association with GA in suspected infectious and inflammatory cases. Therefore, regional anaesthesia should be preferred.

Keywords: Biomarker, Pentraxin-3, General Anesthesia, Spinal Anesthesia

INTRODUCTION

The pentraxin (PTX) family, an acute-phase reactant, has a discoid structure consisting of cyclic pentamers that are highly stable proteins. It has subgroups of long and short PTXs. The standard acute-phase protein, C-reactive protein (CRP), was first defined in the 1930s, with the serum amyloid component (SAP) constituting the short PTXs and pentraxin-3 (PTX3) being the prototype of long PTXs (1). The main structural feature of PTX3 is the presence of an amino-terminal domain, which is 174 amino acids in length, unlike CRP and SAP.

There are differing features not only in the structure of the CRP but also in the source of its secretion. PTX3 is secreted by macrophages, dendritic cells, neutrophils, fibroblasts and vascular endothelial cells within an inflammatory zone, and CRP is secreted by hepatocytes (2). The source of production or secretion of PTX3 depends on the type of stimulant.

PTX3 levels increase in both acute and chronic diseases (3). Recent studies have reported that PTX3 is correlated with the severity of the disease (4, 5), is a good indicator of mortality (6, 7) and is useful in monitoring treatment success (4).

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Moreover, it is a better biomarker that provides earlier warning than CRP and is an indicator of organ dysfunction (8). These advantages observed in infectious cases suggest that PTX3 may become a more widely used marker in the future. However, to date, there is inadequate information about the factors affecting PTX3 levels.

The direct pharmacologic effects of agents used during anaesthesia in terms of the type, duration and depth of anaesthesia and their effects on stress response and the immune system have been studied previously (9–11). Therefore, it is possible that anaesthesia affects PTX3 levels. In this study, we aimed to investigate the effects of two types of anaesthesia applications, general anaesthesia (GA) and spinal anaesthesia (SA), on PTX3 levels.

MATERIALS and METHODS

Study design. The study was approved by the Institutional Ethics Committee of the Clinical Research of Canakkale Onsekiz Mart University (Protocol No: 2015-04, Date: February 18, 2015). The study was conducted in 2015-2016 at Canakkale Onsekiz Mart University Faculty of Medicine Hospital and Canakkale Public Hospital. All participants were pregnant at term and older than 18 years. The patients were excluded if they had an emergency operation, active infectious disease, malignancy, or preeclampsia. The exclusion criteria were age younger than 18 years, emergency surgery, active infection, steroid therapy and malignancy. Sixty patients were divided into two groups.

GA group (n = 30): Caesarean section (C-section) under the GA group. Following pre-oxygenation, 0.5 mg/kg of lidocaine, 2–3 mg/kg of propofol and 0.6 mg/kg of rocuronium bromide were intravenously administered to the patients during the induction of anaesthesia. After the umbilical cord was clamped, 1–2 mg/kg−1 of fentanyl was administered to the patient. Anaesthesia was maintained with 50% N2O and 0.5–0.7 minimal alveolar concentration (MAC) for sevoflurane. Inhalation anaesthesia was terminated at the end of the operation, and decurarization was performed.

SA group (n = 30): C-section under the SA group. Fluid infusion with a balanced crystalloid solution of 15 mL kg−1 was administered to the patients before anaesthesia to prevent maternal hypotension. A total of 10–12 mg of 0.5% hyperbaric bupivacaine + 25 μg fentanyl (total volume of 2.5 ± 0.3 mL) mixture was administered using a 25‐27 G spinal needle for SA. Surgery was performed when the sensory block reached T6‐T8. Intraoperatively, if the systolic arterial pressure decreased to ⩽ 90 mmHg, an intravenous (i.v.) bolus of 5 mg of ephedrine was administered until the systolic blood pressure increased to 100 mmHg. If the heart rate was ⩽ 55 beats min−1, 0.5 mg of i.v. atropine was administered. Age, weight, gravida, parity, gestational age, foetal gender, birth weight and 1–5 min Apgar values of all patients were recorded. Neonatal Apgar evaluation was performed by paediatricians.

Blood samples: For basal values, serum samples were obtained from patients who were about to deliver through C-section during preoperative examination. A second set of serum samples was obtained at 6 h postoperatively, and a third set of serum samples were obtained from all patients at 24 h following the delivery. White blood cell (WBC), neutrophil, lymphocyte, CRP and PTX3 values were measured from the blood samples.

Measurement of plasma PTX3: The samples for the analysis of PTX3 levels were stored at −80°C in small specimen containers. The samples were studied following the completion of serum collection in the biochemistry laboratory of the Canakkale Onsekiz Mart University Faculty of Medicine Hospital. Serum PTX3 levels were determined quantitatively using an enzyme-linked immunosorbent assay (ELISA) using an ELISA microplate strip washer (ELX50; BioTek Instruments, Vinooski, VT, USA) and an ELISA microplate reader (ELX808; BioTek Instruments, USA). PTX3 was analysed using a commercially available kit from MyBioSource Diagnostics (MyBioSource, Inc., San Diego, CA, USA). The minimum detectable dose of PTX3 was up to 0.06 ng/mL. The intra- and inter-assay coefficients of variation for PTX3 were 8% and 12%, respectively. Correlation between laboratory tests results. The correlation of PTX3 with other inflammation indicators, such as WBC, neutrophil, lymphocyte and CRP values, was evaluated for each group.

Statistical analysis: The obtained data were compared using IBM SPSS Statistics 19 software owned by Canakkale Onsekiz Mart University. The variables were investigated using visual (histogram and probability plots) and analytical methods (Kolmogorov–Smirnov test) to determine whether they were normally distributed. Descriptive analyses were presented using the means and standard deviations for normal variables. As the WBC, neutrophil, lymphocyte, CRP and PTX3 values and the patient data were normally distributed; Student's t-test was used to compare these parameters between the SA and GA groups. A t-test was used for the intergroup statistical comparison of the PTX3 levels. The correlation of PTX3 levels with the WBC, neutrophil, lymphocyte and CRP values was evaluated using the Spearman correlation test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patients' characteristics: A significant intergroup difference was not observed in the data related to pregnancy, such as the demographic features of patients, mother's weight, gravida, parity, gestational age, and information related to the baby, such as gender, birth weight and Apgar score. The data are summarised in **Table 1**. The duration of surgery was approximately 50 min for the GA group and 45 min for the SA group. Hypotension was observed in two patients in the SA group and was treated with 5–10 mg of i.v. ephedrine.

Routine laboratory analyses: The mean CRP levels were higher (normal range, 5 mg/L) than those of non-pregnant healthy adults in all groups. Moreover, the CRP levels were higher in consecutive measurements. In the intragroup comparison of CRP levels between the SA and GA groups, all differences were statistically significant ($p < 0.05$). In the intergroup comparison, significant differences were found in the CRP levels between the SA and GA groups at 6 h and 24 h postoperatively. Significant intergroup differences were not found in the WBC, neutrophil, or lymphocyte values. The results are summarised in **Table 2**.

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Table 1. Demographic characteristics of C-section patients under GA or SA, data related to pregnancy and information related to the baby after birth.

	Spinal Anesthesia (n=30)	General Anesthesia (n=30)	p value
Age (years)	27.3 ± 6.2	28.2 ± 7.1	0.84
Maternal weight (kg)	80.6 ± 9.1	73 ± 8,7	0.35
Gravida	2.3 ± 2.1	2.2 ± 1.9	0.70
Parity	1.2 ± 2.0	1.0 ± 0.9	0.14
Delivery (weeks)	38.3 ± 2.6	36.6 ± 3.3	0.17
Male (baby), n (%)	17 (57)	21 (70)	
Birth weight (g)	3475 ± 960	3664 ± 745	0.08
APGAR score 1. min	6.9 ± 1.5	6.2 ± 1.2	0.272
APGAR score 5. min	9.0 ± 1.0	8.5 ± 1.2	0.368

Table 2. Intragroup and intergroup statistical comparison of the WBC, neutrophil, lymphocyte, CRP and PTX3 results.

Parameters		Spinal Anesthesia	General Anesthesia	*p* value
WBC count (x10^3/mL)	*T1 T2 T3*	7.93 ± 1.73 7.43 ± 2.67 8.34 ± 2.64	7.61 ± 1.68 8.16 ± 2.83 8.20 ± 2.60	0.07 0.35 0.26
Neutrophil (x10^3/mL)	*T1 T2 T3*	4.65 ± 1.47 5.17 ± 1.96 5.23 ± 1.91	4.51 ± 1.42 5.3 ± 1.83 4.61 ± 1.37	0.18 0.62 0.51
Lymphocyte (x10^3/mL)	*T1 T2 T3*	2.09 ± 0.89 1.82 ± 1.53 2.23 ± 0.92	2.07 ± 0.83 2.41 ± 1.08 2.28 ± 0.84	0.81 0.16 0.35
CRP (mg/dL)	*T1 T2 T3*	6.5 ± 1.5 9.5 ± 1.7 # 31.6 ± 9.8 # ¥	5.9 ± 1.6 13.1 ± 2.7 # 19.2 ± 5.5 # ¥	0.10 *0.00** *0.00**
Pentraxin-3 (ng/mL)	*T1 T2 T3*	0.13 ± 0.06 0.12 ± 0.04 0.15 ± 0.04 ¥	0.16± 0.06 0.25 ± 0.08 # 0.54 ± 0.09 # ¥	0.83

WBC, white blood cell; CRP, C-reactive protein; T1, before anesthesia; T2, 6 hour after anesthesia; T3, 24 hour after anesthesia.
*: p<0.05 in the intergroup comparison
#: p<0.05 compared to preoperative values in the intragroup comparison
¥: p<0.05 compared to 6th hour after operation values in the intragroup comparison

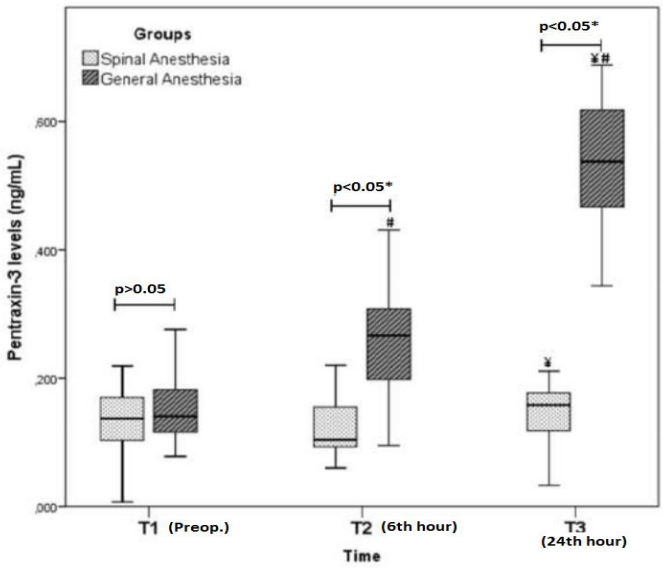

Figure 1. The results of intragroup and intergroup statistical comparison of pentraxin- 3 levels of both groups obtained at the preoperative and postoperative 6 and 24 hour.
*: p<0.05 in the intergroup comparison
#: p<0.05 compared to preoperative values in the intragroup comparison
¥: p<0.05 compared to 6 hour after operation values in the intragroup comparison

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Table 3. Correlation between the PTX3 levels and the WBC, neutrophil, lymphocyte and CRP values.

Parameters		Spinal Anesthesia	General Anesthesia
Pentraxin-3 - WBC	*T1*	0.68	0.87
	T2	0.95	0.85
	T3	0.27	0.61
Pentraxin-3 - Neutrophil	*T1*	0.16	0.93
	T2	0.77	0.87
	T3	0.41	0.30
Pentraxin-3 - Lymphocyte	*T1*	0.17	0.52
	T2	0.53	0.45
	T3	0.93	0.05
Pentraxin-3 - CRP	*T1*	*0.01**	*0.03**
	T2	*0.02**	*0.04**
	T3	0.61	0.09

WBC, white blood cell; CRP, C-reactive protein; T1, before anesthesia; T2, 6 hour after anesthesia; T3, 24 hour after anesthesia; *:p<0.05.

Serum PTX3 levels: The PTX3 values preoperatively were comparable between the two groups ($p > 0.05$). In the intragroup comparison, the decrease in the SA group was not statistically significant ($p > 0.05$), but the increase in the GA group was statistically significant ($p < 0.05$) at 6 h postoperatively compared with the preoperative values.

The PTX3 levels were significantly higher at 24 h postoperatively than at 6 h postoperatively in all groups ($p < 0.05$). The PTX3 levels increased significantly in the GA group, but the increase in the SA group was not statistically significant 24 h postoperatively compared with the preoperative values (**Table 2**). In the intergroup comparison, GA was significantly higher than SA at both 6 h and 24 h postoperatively ($p < 0.05$, **Figure 1**).

Correlation between laboratory test results: The correlation of the calculated differences between the effects of pre- and post-anaesthesia on the PTX3 levels with other inflammatory markers is shown in **Table 3**.

The intragroup changes in the PTX3 levels in both the SA and GA groups did not correlate with the change in the WBC, neutrophil, lymphocyte and CRP measurements ($p > 0.05$, **Table 3**).

DISCUSSION

In this study, PTX3, which is considered a new acute-phase reactant, was observed to be significantly elevated in patients undergoing a C-section through GA during the postoperative period compared with the preoperative period.

PTX3 is a good indicator of the inflammatory response. The setting of an infection has been shown to correlate with the severity of disease (**12**). In addition, it correlates with the success of treatment after antibiotic therapy (**13, 14**). In a 2012 study, Bastrup et al. (**12**) showed that PTX3 levels in patients diagnosed with systemic inflammatory response syndrome (SIRS) correlated with the severity of SIRS, sepsis, severe sepsis, septic shock and mortality. In 2013, Kleber et al. (**15**) found that PTX3 acted as a secondary acute-phase reactant in patients exposed to polytrauma, with the levels significantly increased in a period of 24 h.

These studies emphasise the clinical importance of PTX3 levels in both infectious diseases and trauma. In our study, the PTX3 levels increased more in the GA group than in the SA group. It is advisable to use regional anaesthesia for suspected infectious cases that will undergo surgical procedures. However, data about other factors affecting PTX3 levels are inadequate.

Anaesthesia implementations affect the immune system (**9**). However, to the best of our knowledge, to date, no clinical studies have been conducted on the effects of anaesthesia on PTX3 levels.

In this study, we examined two patient groups giving birth through SA and GA. The PTX3 levels increased significantly in the postoperative period compared with the preoperative period in the GA group. Conversely, the PTX3 levels did not significantly increase in the postoperative period compared with the preoperative period in the SA group.

This effect of GA on the levels of an inflammatory marker (PTX3) may be related to several factors. Research on the effects of volatile anaesthetics on the immune system has generally consisted of animal studies (**16–18**). Volatile anaesthetics in vitro exhibited a dose-dependent inhibitory effect on neutrophil function, reduced the release of cytokines from mononuclear cells, reduced the cell proliferation of lymphocytes and induced apoptosis in lymphocytes (**19–21**). However, measuring the effects of anaesthesia and surgery alone on the immune system in humans is difficult. Many factors, such as medical history and demographic characteristics of the patient, type of surgery, tissue properties and duration of operation, may affect the immune response. Different anaesthetic agents created different effects on the immune system in a study attempting to minimise the effect of surgery in humans (**22**). The effects of volatile anaesthetics on lymphocyte function have been reported to be highly variable. They also inhibit neutrophil chemotaxis and microbicidal oxidative functions in humans (**16, 23**). The effects of propofol have been observed to be generally protective. Mitsuhata et al. demonstrated that sevoflurane application led to the release of cytokines, such as interleukin (IL)-1β and tumour necrosis factor-α by Natural Killer (NK) and NK-like cells (**24**). Nitric oxide administration was

associated with depression in neutrophil function and decreased production of mononuclear cells (28). Our study suggests that the PTX3 increase in group GA may be related to the use of sevoflurane and nitrous oxide as inhalation anaesthesia. Kitamura et al. (25) found that sevoflurane caused lymphopenia in human studies comparing the use of sevoflurane and propofol, whereas propofol was protective against lymphopenia. Schneemilch et al. (16) showed a significant increase in IL-6 levels during and after inhalation anaesthesia.

Their study compared the effects of total i.v. anaesthesia (propofol and sufentanil) with those of inhalational anaesthesia (sevoflurane, fentanyl and N_2O) on the immune system. We used the induction of anaesthesia with propofol and the maintenance of anaesthesia with sevoflurane in the GA group. The increase observed in PTX3 levels, which is consistent with the literature, is likely to be related to sevoflurane. Moreover, we used fentanyl as an analgesic in the GA group. Fentanyl generally increases the number of NK cells but does not contribute to cell activity, which may have affected the PTX3 increase (22).

In our study, to reduce external factors, we included C-section cases with similar durations of surgery, those that avoided the use of drugs because of pregnancy, younger age groups and those that had no additional diseases. Pregnant women who had preeclampsia with high PTX3 levels due to endothelial dysfunction were also excluded from the study (26).

Compared with GA, regional anaesthesia was shown to have a minimal effect on patients' immune system in two recent studies (27, 28). However, there is insufficient information about the effects of regional anaesthesia on PTX3 levels. To the best of our knowledge, our study is the first to investigate PTX3 levels and regional anaesthesia. Again, there is inadequate information on the effect of surgical procedures on PTX3 levels. Nevertheless, no significant difference in PTX3 levels was observed between treated and untreated patients diagnosed with SIRS and sepsis in Bastrup et al.'s study (12). In our study, the insignificant increase in PTX3 levels in the SA group suggests that both SA and surgery slightly affect PTX3 levels. The factors that reduce stress in patients, such as being awake during SA, hearing the sound of a baby and watching the baby, should also not be disregarded.

CONCLUSIONS

During a C-section, patients who were investigated for the effects of GA and regional anaesthesia on PTX3 levels showed the following results:

1. PTX3 levels in the postoperative period compared with the preoperative period significantly increased in patients undergoing a C-section under GA.

2. Changes in PTX3 levels were not observed in the postoperative period compared with the preoperative period in patients undergoing a C-section under SA.

3. The levels of PTX3, which is accepted as an acute-phase reactant, are likely to be elevated in association with GA in the setting of suspected infectious and inflammatory cases. Therefore, regional anaesthesia should be preferred.

Author Contributions: Hatice Betul Altinisik[A,B,C,D,E,F], Fatma Beyazit[C,F], Hakan Turkon[A,C]

A–research concept and design;
B–collection and/or assembly of data;
C–data analysis and interpretation;
D–writing the article;
E–critical revision of the article;
F–final approval of article;.

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