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ORIGINAL ARTICLE

Comparison of the effects of intravenous analgesic agents used in the intraoperative period on pentraxin-3 levels in patients undergoing on-pump coronary artery bypass surgery

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ABSTRACT

Objective: The aim of this study was to compare the effects of fentanyl, dexmedetomidine, and remifentanil on serum pentraxin 3 levels in patients undergoing on-pump coronary artery bypass surgery.

Materials and Methods: In this retrospectively designed study, 36 patients who underwent elective on-pump coronary artery bypass surgery for coronary artery disease in the Cardiovascular Surgery Clinic of our hospital between 01.01.2020 and 31.12.2021 and whose serum pentraxin 3 levels were studied in the pre-operative and post-operative period were included. Patients were divided into 3 groups as fentanyl (Group F), dexmedetomidine (Group D), and remifentanil (Group R) based on the analgesic agent used during the intraoperative period. The data of the patients were obtained by scanning their files and information in the hospital automation system.

Results: Demographic characteristics, duration of anesthesia, cardiopulmonary bypass duration, and aortic cross-clamp duration were similar. When serum pentraxin 3 levels were evaluated within groups, the difference between pre-operative and post-operative results was significant. In the intergroup evaluation, only the results obtained from Group F in the pre-operative period were significant compared to the other groups, but there was no significant difference between the results obtained in the post-operative period.

Conclusion: When the data of this study were evaluated, it was determined that the analgesic agent used in the intraoperative period of on-pump coronary artery bypass surgery did not significantly affect post-operative serum pentraxin 3 levels.

Keywords: Coronary artery bypass surgery, dexmedetomidine, fentanyl, pentraxin 3, remifentanil.

INTRODUCTION

Pentraxin-3 (PTX 3), a current acute phase reactant, was first discovered in the early 1990s, and the human PTX 3 gene is located on chromosome 3q25 [1]. It has been reported to be predominantly present in macrophages, neutrophils, dendritic cells, smooth muscle cells, atherosclerotic lesions, and inflammatory endothelial cells [2,3]. It plays a role in vascular inflammation and endothelial dysfunction through various mechanisms. It is a good indicator of mortality and a useful marker for monitoring treatment success. Studies have confirmed a significant connection between PTX 3 and endothelial dysfunction [4].

The most effective treatment method for atherosclerosis and related coronary artery disease (CAD) is coronary artery bypass graft (CABG) surgery. When performed with the cardiopulmonary bypass

(CPB) pump, it can lead to a systemic inflammatory response that can cause major organ dysfunction [5], adversely affect post-operative outcomes, and even result in systemic inflammatory response syndrome, which can lead to mortality, and an increase in serum PTX 3 levels in the early post-operative period [6].

In addition to the anesthetic agent used, fentanyl, dexmedetomidine or remifentanil are routinely used by intravenous (IV) infusion for analgesic activity during anesthesia maintenance. These agents can exhibit antioxidant and cytoprotective effects to varying degrees in addition to their analgesic activity [7]. It has been shown that the preferred anesthesia management during surgery can be effective on serum PTX 3 levels [8].

In this retrospective study, we aimed to compare the effects of the IV analgesic agents fentanyl, dexmedetomidine, and remifentanil, which were used for anesthesia maintenance in patients undergoing elective on-pump CABG surgery, on post-operative PTX 3 levels. We conducted our study with the hypothesis that dexmedetomidine would have a greater cytoprotective effect.

MATERIALS AND METHODS

This study protocol was approved by the Hacettepe University Non-Interventional Clinical Studies Ethics Committee on May 31, 2022, with decision number GO 22/525.

This retrospective case-control study, which we designed after obtaining ethical approval, was conducted at Hacettepe University Adult Hospital between June 1, 2022, and September 1, 2022. It was planned to include patients who underwent elective on-pump CABG surgery at the Department of Cardiovascular Surgery of Hacettepe University School of Medicine due to CAD between January 1, 2020, and December 31, 2021, and whose serum PTX 3 levels were obtained in the pre-operative and post-operative period. The files of a total of 38 patients were reviewed, and 36 patients with complete data were included in the study. The patients included in the study were divided into three groups: the fentanyl group (Group F), the dexmedetomidine group (Group D), and the remifentanil group (Group R), based on the analgesic agent used during anesthesia maintenance. Blood samples were obtained and evaluated for PTX 3 levels at three different times: pre-operative period (T1), 7th hour post-operatively (T2), and 24th hour post-operatively (T3). Patient data such as age, weight, height, gender, anesthesia management, surgical duration, anesthesia duration, aortic cross-clamp duration, and the agent used for anesthesia maintenance were obtained through scanning the patients files, while laboratory data, including PTX 3 level, were obtained from the database of the hospital.

In addition to the standard ASA monitoring applied to the patients taken to the operating room for surgery, invasive arterial blood pressure, central venous pressure, urinary catheter, body temperature, and near-infrared spectroscopy (NIRS) monitoring, which are routine in our clinic, were also applied. For all patients included in the study, induction and subsequent endotracheal intubation were performed using our clinic's standard anesthesia protocol with midazolam 0.01-0.1 mg/kg, propofol 1-2.5 mg/kg, fentanyl 1-2 mcg/kg, and rocuronium 0.6-1 mg/kg. Fentanyl at a dose of 2 mcg/kg/hour, dexmedetomidine at a dose of 0.4 mcg/kg/hour, or remifentanil at a dose of 0.05 mcg/kg/minute was used intravenously throughout the maintenance period, with one of these agents being started with induction. All patients received 16 mg of IV dexamethasone. Anesthesia was maintained using 2% sevoflurane, 50% O_2/air mixture, and IV fentanyl, dexmedetomidine, or remifentanil. In all cases of CABG surgery, performed on-pump technique, and during the CPB period, anesthesia maintenance was provided through 2% sevoflurane administered via the CPB pump and fentanyl, dexmedetomidine, or remifentanil administered intravenously. After the administration of all anesthetic agents used after surgery was stopped, all patients were transferred to the cardiac surgery intensive care unit while still intubated.

Statistics

Descriptive statistics were used for patient demographic information, anesthesia duration, cardiopulmonary bypass duration, and aortic cross-clamp duration. Continuous variables were presented as means and standard deviations or

medians and interquartile ranges depending on the distribution. Categorical variables were presented as frequencies and percentages. Statistical significance was determined using the chi-square or Fisher's exact test for categorical variables and the Kruskal-Wallis or Friedman test for continuous variables ($p < 0.05$). The Statistical Package for the Social Sciences (SPSS) software package (Version 27.0, IBM, New York, USA) was used for all analyses. Sample size calculation, primary and secondary endpoints, and record details were not applicable to this retrospective study.

RESULTS

A total of 36 participants (30 males, 6 females) were included in this study, and these participants were divided into three groups: the fentanyl group consisted of 13 participants (13 males, 0 females), the dexmedetomidine group consisted of 13 participants (9 males, 4 females), and the remifentanil group consisted of 10 participants (8 males, 2 females). The average age of the participants was calculated as 57.92 (±9.97).

Demographic and Clinical Characteristics

The basic demographic and clinical characteristics of the study participants were carefully evaluated (Table 1). The average ages of the participants did not show a significant difference between the fentanyl group (mean age 54.00 ± 8.84 years), the dexmedetomidine group (mean age 58.85 ± 6.79 years), and the remifentanil group (mean age 61.80 ± 13.44 years) ($p = 0.164$). Similarly, there was no significant difference in gender distribution among the three groups ($p = 0.103$).

When anesthesia duration, cardiopulmonary bypass duration, and aortic cross-clamp duration were examined in detail, the average anesthesia duration was 329.23 ± 64.48 minutes, the average cardiopulmonary bypass duration was 114.00 ± 40.44 minutes, and the average aortic cross-clamp duration was 67.54 ± 24.64 minutes for the fentanyl group. For the dexmedetomidine group, the average anesthesia duration was 352.31 ± 73.75 minutes, the average cardiopulmonary bypass duration was 116.00 ± 47.00 minutes, and the average aortic cross-clamp duration was 68.31 ± 31.69 minutes. In the remifentanil group, the average anesthesia duration was 318.00 ± 69.21 minutes, the average cardiopulmonary bypass duration was 105.50 ± 26.74 minutes, and the average aortic cross-clamp duration was 64.20 ± 17.32 minutes. These analysis results indicate that the baseline characteristics of the participants in each group were statistically similar ($p = 0.480$; $p = 0.809$; $p = 0.925$).

Table 1. Demographic characteristics of participants, anesthesia duration, cardiopulmonary bypass duration, aortic cross-clamp duration, and pentraxin 3 levels

	Fentanyl Group (n=13)	Deksmedetomidin Group (n=13)	Remifentanil Group (n=10)	Total (n=36)	p
Age	54.00(±8.84)	58.85 (±6.79)	61.80(±13.44)	57.92(±9.97)	0.164
Sex	F=0 (0%) M=13(100%)	F=4 (30.0%) M=9 (69.2%)	F=2 (20%) M=8 (80%)	F=6 (16.7%) M=30 (83.3%)	0.103
Anesthesia duration	329.23 (±64.48)	352.31 (±73.75)	318.00 (±69.21)	334.44 (±68.76)	0.480
Cardiopulmonary bypass duration	114.00 (±40.44)	116.00 (±47.00)	105.50 (±26.74)	112.36 (±39.00)	0.809
Aortic cross-clamp duration	67.54 (±24.64)	68.31 (±31.69)	64.20 (±17.32)	66.89 (±25.15)	0.925
Pentraxin 3 levels					
T1	1.79 (0.66-2.55)	0.77 (0.10-1.48)	1.06 (0.22-4.77)	1.16 (0.10-4.47)	**<0.001**
T2	46.27 (25.86-183.13)	60.81 (34.03-141.87)	52.16 (21.98-197.49)	54.25 (21.98-197.49)	0.615
T3	19.95 (5.49-179.18)	18.38 (10.31-57.53)	25.79 (6.13-68.31)	20.80 (5.49-179.18)	0.604

Age information is given in years, anesthesia, cardiopulmonary bypass , and aortic cross-clamp durations are expressed in minutes. Pentraxin 3 levels are recorded as ng/ml. When indicating gender, "F" represents female, and "M" represents male. T1 represents the pre-operative period; T2 represents the post-operative 7th hour; T3 represents the post-operative 24th hour. Age, anesthesia duration, cardiopulmonary bypass duration, and aortic cross-clamp duration were analyzed using the ANOVA method. The gender variable was evaluated using the Chi-square test. The values were provided as mean (± SD), median (min–max).

Table 2. Comparison of pentraxin 3 levels within groups

Group		n	x^2	df	p
Fentanil	Difference 2-1	13	21.385	2	0.000
	Difference 3-2				
	Difference 3-1				
Deksmedetomidin	Difference 2-1	13	26.000	2	<0.001
	Difference 3-2				
	Difference 3-1				
Remifentanil	Difference 2-1	10	15.800	2	0.000
	Difference 3-2				
	Difference 3-1				

The Friedman test was used for analysis. Difference 2-1 represents the difference in pentraxin 3 levels between pre-operative and post-operative 7th hour, Difference 3-1 represents the difference in pentraxin 3 levels between pre-operative and post-operative 24th hour, and Difference 3-2 represents the difference in pentraxin 3 levels between post-operative 7th hour and post-operative 24th hour.

Table 3. Comparison of pentraxin 3 levels between groups

	Group	n	Mean	df	x^2	p
Difference 2-1	Fentanil	13	18.08	2	1.060	.588
	Dexmedetomidin	13	20.69			
	Remifentanil	10	16.20			
Difference 3-2	Fentanil	13	18.08	2	3.365	.186
	Dexmedetomidin	13	20.69			
	Remifentanil	10	16.20			
Difference 3-1	Fentanil	13	18.08	2	0.660	.719
	Dexmedetomidin	13	20.69			
	Remifentanil	10	16.20			

The Kruskal-Wallis test was applied in the analysis. Difference 2-1 represents the difference in pentraxin 3 levels between pre-operative and post-operative 7th hour, Difference 3-1 represents the difference in pentraxin 3 levels between pre-operative and post-operative 24th hour, and Difference 3-2 represents the difference in pentraxin 3 levels between post-operative 7th hour and post-operative 24th hour.

Pentraxin 3 Levels

Pre-operative PTX 3 levels showed a significant difference between the groups (Table 1) ($p < 0.001$). In the pre-operative period, the PTX 3 level of the fentanyl group was 1.79 ng/ml (95% CI: 0.66 – 2.55), the PTX 3 level of the dexmedetomidine group was 0.77 ng/ml (95% CI: 0.10 – 1.48), and the PTX 3 level of the remifentanil group was 1.06 ng/ml (95% CI: 0.22 – 4.77).

Comparison of Pentraxin 3 Levels Within Groups

In the fentanyl group, a significant differentiation in PTX 3 levels over time was observed (χ^2 (df = 2, n = 13) = 21.385, $p < 0.001$). Similarly, a significant change was observed in the dexmedetomidine group (χ^2 (df = 2, n = 13) = 26.000, $p < 0.001$). In the remifentanil group, a similar significant change was also observed (χ^2 (df = 2, n = 13) = 15.800, $p < 0.001$). These analysis results are shown in Table 2.

Comparison of Pentraxin 3 Levels Between Groups

Differences in PTX 3 levels obtained within three different time periods did not show a significant variation between the groups (Table 3). The difference between the post-operative 7th hour and the pre-operative period did not show a significant difference between the groups (χ^2 (df = 2, n = 36) = 1.060, $p > 0.05$). Similarly, the difference between the post-operative 24th hour and 7th hour did not show a significant difference between the groups (χ^2 (df = 2, n = 36) = 3.365, $p > 0.05$). Finally, the difference between the post-operative 24th hour and the pre-operative period did not create a significant difference between the groups (χ^2 (df = 3, n = 36) = 0.660, $p > 0.05$). These findings indicate that changes in PTX 3 levels during the specified time periods did not show a significant difference between the groups. Figure 1 shows the PTX 3 levels measured at three different time periods on the graph.

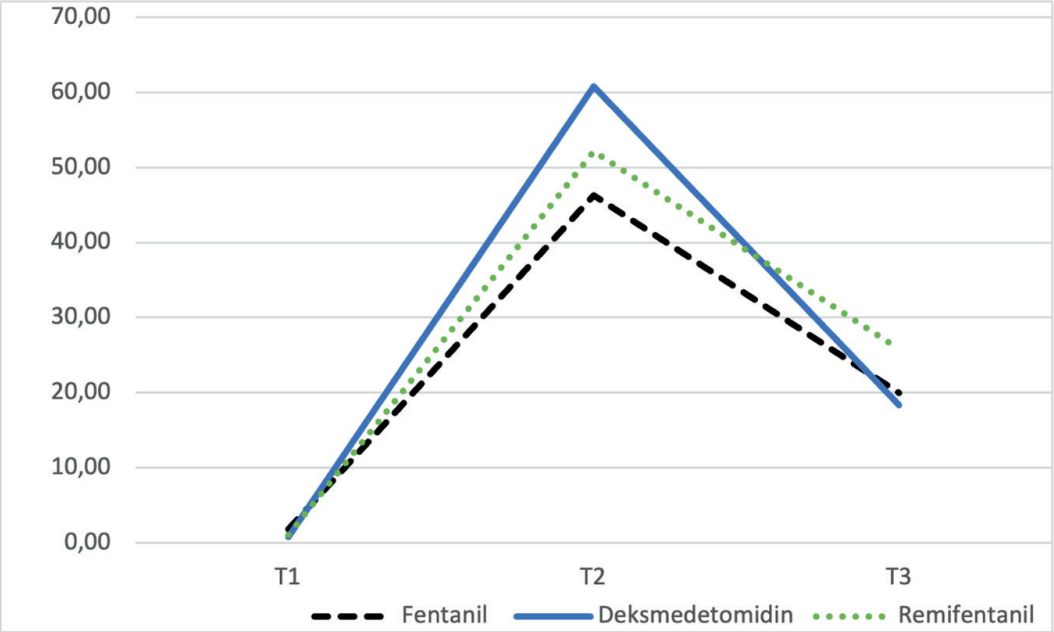

Figure 1. Changes in pentraxin 3 levels over time among groups
T1: Pre-operative, T2: Post-operative 7th hour, T3: Post-operative 24th hour.

DISCUSSION

In this study, we investigated the effects of the IV analgesic agents fentanyl, dexmedetomidine, and remifentanil, used for anesthesia maintenance during surgery, on post-operative PTX 3 levels in patients undergoing on-pump CABG surgery. As far as we know, this study is the first clinical study to investigate the effects of fentanyl, dexmedetomidine, and remifentanil on serum PTX 3 levels in patients undergoing on-pump CABG surgery. In the intra-group evaluations, it was found that the differences in PTX 3 levels measured at different time points were significant in all three groups. In the inter-group comparisons, significant differences were observed among the results obtained at the T1 time point (Table 1), while when evaluating the differences between time points, no significant differences were found among the results (Table 2).

In a study conducted by Jaworski et al. [9], which evaluated post-operative PTX 3 kinetics in children undergoing on-pump cardiac surgery due to congenital heart diseases, it was observed that PTX 3 levels peaked on the first post-operative day and then decreased to baseline values in the following days. Similarly, in a study by Hamada et al. [5], investigating the effect of dexmedetomidine on PTX 3 in patients undergoing on-pump cardiac surgery, it was observed that both the control and study groups reached their highest serum PTX 3 levels on the first post-operative day. Wang et al. [10], as a result of a study focusing on children with congenital heart diseases undergoing on-pump cardiac surgery, suggested that CPB could lead to an increase in serum PTX 3 levels. Consistent with the literature, our study also showed that serum PTX 3 levels reached their highest point at the 7th hour post-operatively and decreased to lower levels by the 24th hour post-operatively.

Altınışık et al. [8] compared general anesthesia and spinal anesthesia methods in their study evaluating the effects of anesthesia methods applied for cesarean section surgery on PTX 3. They found that serum PTX 3 levels increased significantly over time in the group receiving general anesthesia, while the difference in serum PTX 3 levels between time points was not significant in the spinal anesthesia group. Another study focused on the effect of dexmedetomidine on PTX 3 in patients undergoing on-pump cardiac surgery, suggesting that dexmedetomidine infusion could decrease PTX 3 levels after cardiac surgery with CPB [5]. In our study, while intra-group evaluations showed significant changes in PTX 3 levels over time, inter-group comparisons revealed no significant differences in PTX 3 levels between the T2 and T3 time points. Therefore, our results indicate that there were no superior effects of the administered agents on PTX 3 levels during the intraoperative period.

As a limitation of our study, it could be considered that blood samples were taken only twice in the post-operative period, and the last sample was taken 24th hour post-operatively. It would have been possible to evaluate how the results changed in the long term by evaluating them in a longer period and with more samples in the post-operative period. In addition, standardization could have been better achieved by homogenizing the groups with respect to comorbidities.

CONCLUSION

In conclusion, considering the data obtained from this study, it was observed that the IV analgesic agents fentanyl, dexmedetomidine, or remifentanil used for anesthesia maintenance during surgery did not have a significant effect on post-operative PTX 3 levels, and it was concluded that there was no superiority among them. We believe that randomized controlled prospective studies with larger group sizes are needed to confirm our observations.

Author contribution

Study conception and design: Mİ and BÇ; data collection: Mİ and MT; analysis and interpretation of results: Mİ, MT and BÇ; draft manuscript preparation: Mİ and MT. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Non-Interventional Clinical Studies Ethics Committee (Protocol no. GO 22/525).

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Conflict of interest

The authors declare that there is no conflict of interest.

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