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CHANGES IN TRYPTASE LEVELS DURING CARDIAC SURGERY IN PATIENTS AT LOW RISK FOR ALLERGIC REACTIONS

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Ключові слова: *гіперчутливість, анестезія, кардіологічні процедури, протаміни, побічні ефекти, триптази*

Abstract. Changes in tryptase levels during cardiac surgery in patients at low risk for allergic reactions. **Menekse Oksar**, **Hasibe G. Baytan, Selim Turhanoglu, Tayfun Aybek, Nazife Y. Ardicoglu, Oguzhan Ozcan.** *Tryptase test can be used as a clinical marker of mast cell activation. The present study is was aimed to identify variations in serum tryptase levels and their possible relationships with allergic reactions to protamine in low-risk patients undergoing cardiac bypass surgery. Thirty patients according to American Society of Anesthesiologists physical status III who underwent cardiac bypass surgery were enrolled. This prospective, non-randomised, clinical study was conducted in an operating room. Venous blood samples for tryptase measurements were obtained from cardiac bypass surgery patients upon admission to the operating room and immediately before and 30 min after the initiation of protamine administration. Signs of allergic reactions were recorded and management steps based on rapid effect response-based clinical assessments for diagnosis and treatment decisions during protamine administrations were described. Serum tryptase levels and clinical signs of allergic reactions, primarily mean arterial pressure (MAP), were recorded. Serum tryptase levels increased significantly and progressively during the bypass procedure (study power, 80%; sample size, 28; power of analysis, 99.8% with α=0.05); however, tryptase levels did not reach a sufficiently high level to confirm an allergic reaction. The MAP and heart rate decreased in 50% of the patients. Although tryptase increased significantly when compared with baseline levels, protamine-associated increases were not significant and failed to provide an unequivocal indication of an allergic response to protamine.*

Реферат. Зміни рівня триптази під час операції на серці в пацієнтів з низьким ризиком алергічних реакцій. Менексе Оксар, Хасібе Г. Байтан, Селім Турханоглу, Тайфун Айбек, Назіфе Й. Ардікоглу, Огужан Озджан. *Тест на триптазу можна використовувати як клінічний маркер активації тучних клітин. Це дослідження мало на меті виявити варіації рівнів триптази в сироватці крові та їх можливий зв'язок з алергічними реакціями на протамін у пацієнтів з низьким ризиком, які перенесли операцію серцевого шунтування. Було зареєстровано 30 пацієнтів із фізичним статусом III за класифікацією Американського товариства анестезіологів, які перенесли операцію серцевого шунтування. Це проспективне нерандомізоване клінічне дослідження було проведено в операційній. Зразки венозної крові для вимірювання триптази були взяті в пацієнтів з операцією серцевого шунтування при надходженні в операційну, безпосередньо перед і через 30 хвилин після початку введення протаміну. Було зареєстровано ознаки алергічних реакцій та описано етапи лікування на основі швидкої клінічної оцінки відповіді для діагностики та лікування під час введення протаміну. Реєстрували рівень триптази в сироватці крові та клінічні ознаки алергічних реакцій, насамперед середній артеріальний тиск (САТ). Рівні триптази в сироватці крові значно та прогресивно зростали під час процедури шунтування (потужність дослідження 80%; розмір вибірки 28; потужність аналізу 99,8% з α=0,05); однак рівні триптази не досягли достатньо високого рівня, щоб підтвердити алергічну реакцію. САТ і частота серцевих скорочень знизилися у 50% пацієнтів. Хоча рівень триптази суттєво зріс порівняно з вихідним рівнем, підвищення, пов'язане з протаміном, не було значним і не змогло забезпечити однозначну ознаку алергічної реакції на протамін.*

Protamine, a highly cationic protein [1] neutralises the effects of heparin [2, 3] after a major cardiovascular surgery [4, 5]. Unfortunately, protamine treatment causes haemodynamic instability that is strongly associated with adverse postoperative outcomes [6]. The reported risk factors independently associated with adverse events are neutral protamine Hagedorn insulin use, fish allergy and a history of non-protamine medication allergy [7]. Adverse events occurred in 12.9% of patients undergoing cardiopulmonary bypass; 13% of these events were attributed to protamine in the medical records and 2.4% were reported to the adverse drug reporting programme [8].

Mature tryptase is a neutral serine protease localised in mast cell granules and on mast cell activation, the mature and active tetrameric enzyme is released with other mediators [9, 10]. In humans, several isoenzymes are known, including α, β, γ, δ isoenzymes. β tryptase is primarily stored in human mastocytes and further classified into βI, βII and βIII. βI and βII differ only in one aminoacid at their glycosylation site, whereas βIII differs in an additional three aminoacids compared with βI and βII [11]. The total serum tryptase level increases after severe allergic reactions and anaphylactoid reactions [12]. Circulating tryptase mainly involves inactive pro-β-tryptase, which is secreted constitutively rather than stored in granules (as with mature tryptase), and its level may temporarily increase during severe systemic allergic reactions and can be used for diagnostic confirmation [13, 14]. High baseline tryptase levels are also a risk factor for allergic reactions [15-17]. Additionally, a temporary increase in mature serum tryptase can be used to distinguish IgE-mediated reactions from non-IgE-mediated reactions [17, 27].

Intravenous protamine can cause acute severe reactions that include rash, urticaria, bronchospasm, elevated pulmonary-artery pressure, and hypotension that leads to shock and death [18, 19, 20]. Moderate and life treating systemic hypotension can occur in grade II- III preoperative anaphylaxis [21]. Systemic hypotension can occur due to a protamine reaction [6, 22]. However, although systemic hypotension can be associated with major adverse events, [6, 28] it cannot be clinically confirmed as a reaction to protamine unless it results in severe shock and required vasopressor therapy additionally to fluid administration.

The present study is aimed to identify variations in serum tryptase levels and their possible relationships with allergic reactions to protamine in low-risk patients undergoing cardiac bypass surgery.

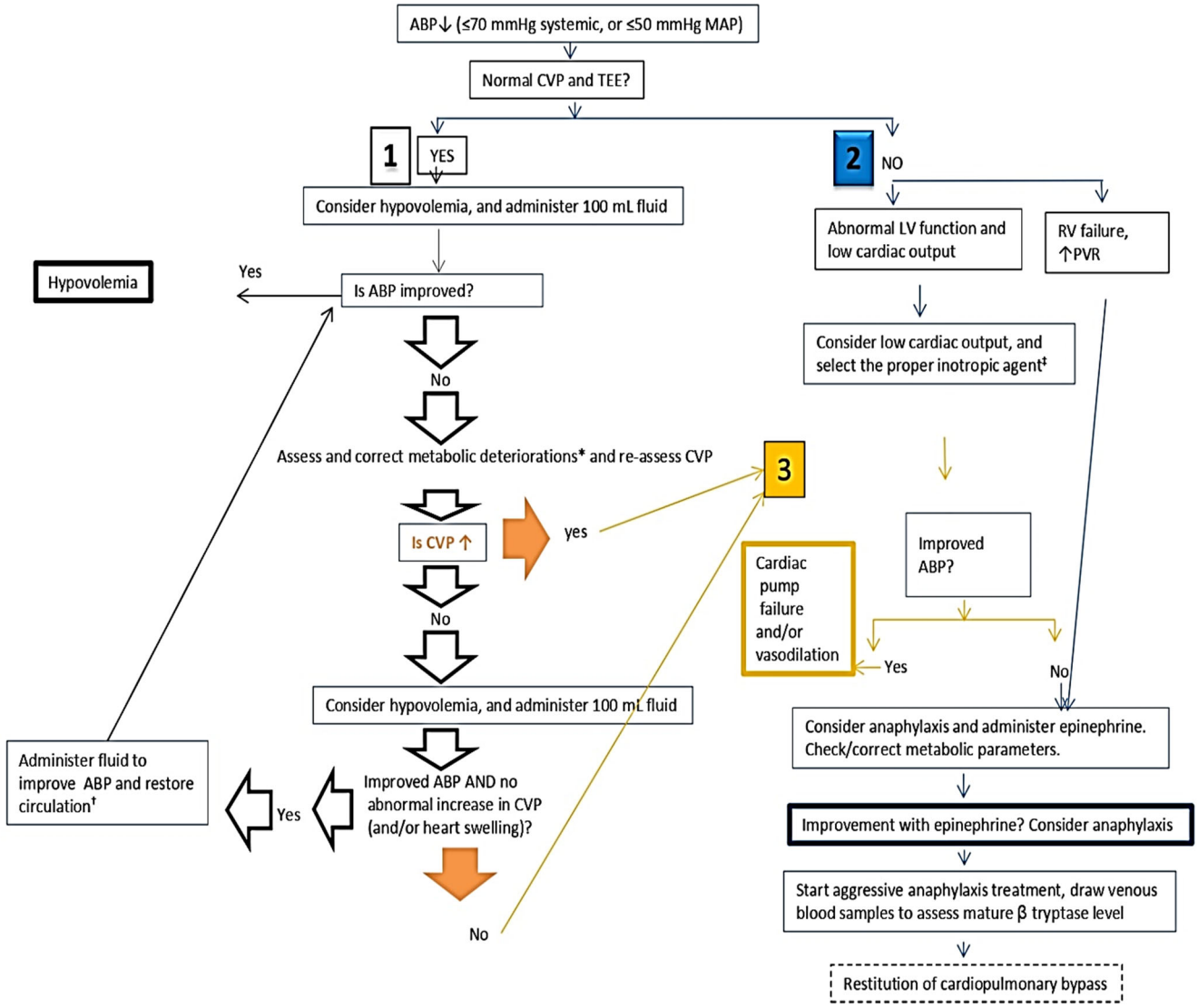
MATERIALS AND METHODS OF RESEARCH

Patient monitoring included the following examinations: (a) routine 5-lead electrocardiography, (b) DII and V5 monitoring during the surgery, (c) left radial arterial cannulation and invasive blood pressure monitoring, (d) right internal jugular vein catheterisation and central venous pressure monitoring, (e) transesophageal echocardiography, (f) pulse oximetry, (g) capnography, and (h) bispectrality index monitoring. Anaesthesia, including midazolam (0.1 mg kg^{-1}), fentanyl (10 μg kg^{-1}), and rocuronium (0.6 mg kg^{-1}), was administered, and patients received 6% desflurane in 50% oxygen (balance air). Systemic heparinisation was achieved using a dose of 350 U kg^{-1}, and additional doses were administered when required. Fentanyl, midazolam and rocuronium were administered through a cardiac pump during bypass surgery, and the activated clotting time (ACT) was monitored. Protamine (PROMIN; 5000 IU per 5 mL, VEM Pharmaceutical Industry and Limited Company, Istanbul, Turkey) was administered after weaning from cardiopulmonary bypass (1 mg per 100-U heparin) to control the ACT. Fluid/erythrocyte suspensions, whole blood, fresh frozen plasma, inotropic agents and/or vasopressors were administered, when required.

The applicable clinical characteristics that could be considered as systemic signs of allergic reactions to medication were assessed; skin signs were recorded in addition to cardiovascular indications of allergic reactions to protamine. Clinical signs of an adverse reaction were as follows: a decrease in the MAP from the critical level occurring within minutes, which was persistent and required intervention (critical MAP limit: ≤50 mm Hg), a change in heart rate (HR) (bradycardia <60 beats min^{-1} or tachycardia >100 beats min^{-1}), and skin rash. Treatment consisted of fluid administration initially, followed by administration of inotropic and/or vasopressor agents. The results were assessed by observing improvements in the cardiovascular signs of allergic reactions using clinical monitoring data (Fig.). During recovery of the left ventricle and restoration of spontaneous circulation, the differential diagnosis and strategy for treating low cardiac output were determined according to the treatment-response steps cautiousyly. Data regarding the administration of blood products, positive inotropic agents and vasopressor agents were collected.

Venous blood samples for tryptase measurement were obtained on admission to the operating room (OR), immediately before protamine administration and, on average, 30 min after the initial protamine administration. The blood samples were centrifuged, and the serum was stored at -20°C until tryptase assays were performed (within 7-10 days of surgery). Total tryptase levels (α- and β-tryptase) were measured using Immuno CAP Tryptase kits (Phadia, Uppsala, Sweden). An elevated mature β-tryptase level was defined as a level >11.5 μg L^{-1}, in

accordance with the reference value provided by Phadia. Serum tryptase levels indicative of mild reactions and anaphylaxis were >11.5-25 μg L^{-1} and >25 μg L^{-1}, respectively. MAP and HR were recorded every 5 minutes during protamine administration in order to not miss any possible changes in MAP and HR, and every 10 minutes after completion the administration for 60 minutes in total.



ABP – arterial blood pressure; MAP – mean arterial pressure; CVP– central venous pressure; TEE – transesophageal echocardiography; LV – left ventricle; RV – right ventricle; PVR – pulmonary vascular resistance. * – Possible metabolic deteriorations: 1. Low arterial pH: a) Increase in lactate (lactic acidosis); b) Low HCO3; 2. Hypokalemia and hyperkalemia; 3. Hypocalcemia; 4. Hypoglycemia and hyperglycemia (Clinical points that need to be evaluated: Low body temperature and concomitant oliguria/anuria; Abnormal increase in CVP; Poor left ventricular function; Vasodilation).

Flow chart for management of hypotension during cardiac bypass surgery: Differential diagnosis of overlapping syndromes

Frequencies were calculated for categorical variables, and descriptive statistics, including the mean and median, were calculated for continuous variables. Shapiro–Wilk normality tests were used to assess the distribution of tryptase levels. Nonparametric tests were used to compare medians in the absence of normal distributions. The change in tryptase levels and other differences between more than 2 dependent groups were analysed using the Friedman test. Associations between continuous variables were assessed using Spearman's correlation coefficients. Multivariate tests were used to calculate the analysis power through repeated measurements of tryptase. The G* Power 3.1 package was used to calculate the study power. Additionally, the association between the administration of blood products and tryptase levels was analysed. All statistical analyses were performed using SPSS (version 22; IBM Corp., Armonk, NY, USA).

This non-randomised, prospective study of serum tryptase levels was approved by our institutional ethics board (13 February 2014, approval number 5) and was supported by institutional funds. Thirty patients according to American Society of Anaesthesiologists physical status III, who underwent cardiac bypass surgery, were enrolled in this study. All patients provided written informed consent. Patients who received protamine with insulin and those with a history of drug allergies or atopy were excluded. Additionally, to avoid confusion during recovery from bypass, those with left ventricular dysfunction having an ejection fraction of <40% were excluded. Premedication was not administered to any patient. Research was conducted in accordance with the principles of bioethics set out in the WMA Declaration of Helsinki – "Ethical principles for medical research involving human subjects" and "Universal Declaration on Bioethics and Human Rights" (UNESCO).

RESULTS AND DISCUSSION

Patient demographics, haemodynamic changes, tryptase levels and other clinical variables relating to potential allergic reactions with their values as range, mean ± standard deviation or patients' number and percentages are listed in Table 1. Following protamine administration, 50% of the patients showed decreases in HR and MAP.

Table 1

Patient demographics and intraoperative treatments

Variable	Distribution	Value
Female/male[a]	**12/18**	**40.0/60.0**
Age (years)[b]	**33-82**	**59.13 ± 10.875**
Weight (kg)[b]	**65-100**	**81.70 ± 8.707**
BMI[c] (kg m^{-2})[b]	**24.22-37.11**	**28.97 ± 2.928**
HR[d] after PROTAMINE[e]		
No decrease/or decrease[f]	**15/15**	**50.0/50.0**
MAP[g] after PROTAMINE		
No decrease/decrease[h]	**15/15**	**50.0/50.0**
RBC[i] (units)		
0/1/2/3/4	**14/3/11/1/1**	**46.7/10.0/36.7/3.3/3.3**
Whole blood (units)		
0/1	**28/2**	**93.3/6.7**
FFP[j] (units)		
0/1/2	**23/3/4**	**76.7/10.0/13.3**
Glucose/insulin		
No/Yes	**29/1**	**96.7/3.3**
Dopamine		
No/Yes	**21/9**	**70.0/30.0**
Dobutamine		
No/Yes	**29/1**	**96.7/3.3**
Norepinephrine		
No/Yes	**29/1**	**96.7/3.3**

Notes: all data are expressed as numbers and percentages except for b – range, mean ± standard deviation; c – body mass index; d – heart rate; e – protamine; f – decrease from 60/min; g – mean arterial pressure; h – decreases from 50 mmHg; i – packed red blood cells; j – fresh frozen plasma.

Statistical differences in SBP, MAP and HR after protamine administration are presented in Tables 2, 3 and 4 for multiple surgery times. There were significant differences between the systolic blood pressure (SBP) measurements performed at different time points ($p<0.001$) (Table 2). There were significant differences between MAP measurements performed at different time points ($p<0.001$) (Table 3). There were significant differences between HR measurements performed at different time points ($p<0.001$) (Table 4).

Table 2

Intraoperative changes in systolic blood pressure (SBP)[a] measurements before and after starting protamine administration

SBP (n=30)	Median	Min.-Maks.	Confidence Interval (%95)	Friedman	p
T_0.SBP Protamine 0	77.00	65-120	79.69-94.65	182.625	0,000*** Fark: T_0- T_5, T_6, T_7, T_8 T_1- T_4, T_5, T_6, T_7, T_8 T_2- T_5, T_6, T_7, T_8 T_3- T_6, T_7, T_8 T_4- T_7, T_8 T_5- T_8
T_1.SBP Protamine 5	71.00	50-120	72.12-92.57		
T_2.SBP Protamine 10	78.00	66-120	81.52-97.24		
T_3.SBP Protamine 15	84.00	70-120	85.85-100.36		
T_4.SBP Protamine 20	88.00	70-122	87.56-101.96		
T_5.SBP Protamine 30	90.00	70-125	91.05-105.02		
T_6.SBP Protamine 40	97.00	68-125	93.26-107.15		
T_7.SBP Protamine 50	107.50	74-130	98.98-112.19		
T_8.SBP Protamine 60	111.50	80-130	103.25-115.99		

Notes: a – systolic blood pressure; b – SBP measurement sequence numbers for the surgical time points; * – $p<0.05$; ** – $p<0.01$; *** – $p<0.001$.

Table 3

Intraoperative changes in mean arterial pressure (MAP)[a] before and after starting protamine administration

Median	Min.-Maks.	Confidence Interval (%95)	Friedman	p
59.50	43-93	57.33-68.26	150.571	0,000*** Fark: T_0- T_5, T_6, T_7, T_8 T_1- T_4, T_5, T_6, T_7, T_8 T_2- T_5, T_6, T_7, T_8 T_3- T_7, T_8 T_4- T_7, T_8 T_5- T_8
53.00	37-93	54.28-67.38		
58.50	49-91	58.69-69.51		
62.00	50-91	61.53-71.37		
64.50	50-92	62.31-71.96		
66.50	51-93	64.3-73.76		
70.50	51-94	65.57-74.84		
71.50	52-95	68.27-77.11		
74.00	53-95	69.66-78.62		

Notes: a – mean arterial pressure; b – difference between the MAP measurement sequence numbers for the surgical time points; * – $p<0.05$; ** – $p<0.01$; *** – $p<0.001$.

Table 4

Intraoperative changes in heart rate (HR)[a] before and after starting protamine administration

HR (n=30)	Median	Min.-Maks.	Confidence Interval (%95)	Friedman	p
T_0.HR Protamine 0	62.00	45-90	59.94-69.79	84.660	0,000*** Fark: T_0- T_4, T_5, T_6, T_7, T_8 T_1- T_2, T_3, T_4, T_5 T_1- T_6, T_7, T_8
T_1.HR Protamine 5	58.50	40-105	55.57-68.43		
T_2.HR Protamine 10	78.00	60-115	71.84-81.26		
T_3.HR Protamine 15	79.00	62-118	73.48-82.38		
T_4.HR Protamine 20	80.00	62-115	73.76-82.38		
T_5.HR Protamine 30	80.00	64-115	76.62-85.31		
T_6.HR Protamine 40	80.00	64-100	77.71-83.81		
T_7.HR Protamine 50	80.00	64-99	78.97-84.48		
T_8.HR Protamine 60	80.00	64-122	80.03-87.56		

Notes: a – heart rate; b – HR measurement sequence numbers for the surgical time points; * – p<0.05; ** – p<0.01; *** – p<0.001.

Progressive increases in serum tryptase levels were observed from the time of OR admission (T1) to immediately before protamine administration (T2) and 30 min after the initial protamine administration (T3; p<0.001, Friedman test). Significant differences were observed between baseline tryptase levels and both intraoperative measurement points (T1 vs. T2, p<0.001; T1 vs. T3, p<0.001); however, no significant difference was observed between the tryptase levels immediately before and 30 min after protamine administration (T2 vs. T3, p>0.05) (Table 5). One patient had elevated tryptase levels (>11.5 μg L^{-1}) at T2 and T3, and his baseline levels were also at the upper limit of the normal range (11.5 μg L^{-1}). Increases in tryptase levels from T1 to T2 (p<0.011) and from T1 to T3 (p<0.020) were significantly greater in female patients than in male patients (Table 6). The power to detect differences in tryptase levels was 99.8%, with α=0.05. The study power was calculated as 80%, and the sample size was 28 throughout changes in tryptase repeated measurements (effect size f, 0.25; α, 0.05). No significant linear relationships were found between tryptase levels and the use of erythrocyte suspension, whole blood, or fresh frozen plasma (p>0.05).

Table 5

Changes in serum tryptase levels (μg L^{-1}) over multiple measurements

	N	Median	Min–max	Chi-square	P	Difference among dependent groups
(T1)	30	3.41	1.2-11.5	39.200	0.000	(1-2, 1-3)*
(T2)	30	4.13	2.29-12.70			
(T3)	30	4.87	2.20-12.30			

Notes: T1 – on admission to the operating room: T2 – immediately before protamine administration: T3 – 30 min after the initial protamine administration; * – groups on the left side of the ranges significantly differ from those on the right side; no statistically significant differences between groups on the right side.

Table 6

Descriptive statistics for blood pressure and heart rate

Cardiac bypass

	Before cardiac bypass							After weaning from the cardiac bypass						
	0*	10*	20*	30*	40*	50*	60*	0*	10*	20*	30*	40*	50*	60*
	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD
SBP	145.63± 13.28	120.97 ±13.94	83.9± 15.1	94.33± 18.99	95.9±1 4.75	90.2±1 3.36	83.47± 9.76	86.67± 19.52	88.73± 20.61	94.13± 18.9	97.37± 18.41	99.53± 18.31	104.93 ±17.44	108.83 ±17.01
DBP	93.6± 10.83	75.63± 16.85	51.37± 13.68	58.47± 12.32	56.4±1 0.36	51.13± 8.67	42.8±6. 13	50.63± 12.51	51± 12.07	52.77± 10.73	53.93± 10.91	54.6± 10.75	55.4± 10.89	56.31± 11
MAP	110.93± 11.12	90.83± 15.02	62.2± 13.57	70.43± 13.47	69.4±1 0.39	64.23± 9.5	56.23± 6.31	62.6± 14.15	63.63± 14.21	66.63± 12.77	68.5± 12.56	69.63± 12.38	72.1± 11.88	73.53± 12.04
HR	126.97± 13.45	100.7± 17.78	82.3± 13.26	83.93± 13.84	81.1±1 0.2	77.73± 8.91	76.83± 5.51	64.7± 12.76	77.27± 12.79	78.4± 11.29	80.87± 11.23	80.67± 7.89	81.67± 7.13	83.67± 9.76

Note. * – Min.

Tryptase levels increased significantly before protamine administration intraoperatively rather than following protamine administration that we expected to demonstrate. This observation is consistent with the finding in a study by Krishna et al. [15] which demonstrated that this phenomenon may be related to the use of other drugs that can evoke allergic responses, such as rocuronium, midazolam, fentanyl, antibiotics and heparin. Blood products also might be a reason to the increase in tryptase levels in this period in our study population. Tryptase levels continued to increase after protamine administration; however, they did not reach the threshold indicative of an allergic reaction to protamine (allergic reaction, 11.5 μg L^{-1}; anaphylaxis, 25 μg L^{-1}), except in 1 patient who had high baseline serum tryptase levels. Significantly elevated baseline serum tryptase has been shown to be associated with adverse reactions, and anaphylaxis was more common in patients with elevated baseline serum tryptase than in those without elevated baseline serum tryptase (21% vs. 14%) [16]. Baseline tryptase levels were reported to be associated with age and IgE levels [23]. Additionally, severe reactions were reported to be associated with lower IgE, older age, cardiovascular disease and baseline serum tryptase ≥11.4 μg L^{-1} [24]. However, Borer-Reinhold et al. reported that even in cases with low absolute tryptase levels, an increase in the tryptase level by ≥135% of the baseline level during a suspected hypersensitivity reaction indicated mast cell activation [25]. In our study, although one patient had high tryptase levels that continued to increase after protamine administration from 11.50 to 12.70 μg L^{-1}, the increase was not high enough to suspect anaphylaxis. A lower tryptase threshold was reported to be associated with life-threatening allergic reactions in cardiovascular surgery cases [26]. For differentiating between life-threatening allergic reactions under anaesthesia and cases of shock or cardiac arrest, the authors determined that the thresholds for plasma histamine and tryptase were 6.35 nmol L^{-1} and 7.35 μg L^{-1}, respectively. Therefore, the authors suggested decreasing the thresholds for histamine and tryptase. In our study, two patients with tryptase levels of 9.31 and 7.74 μg L^{-1} just before protamine administration exceeded the tryptase threshold level suggested by these authors, with levels increasing to 11.10 and 8.29 μg L^{-1}, respectively after protamine administration. Because of high tryptase levels before protamine administration, these increases can be attributed to protamine administration as well as other potential allergic intraoperative drugs; three patients exceeded the threshold level suggested by these authors after protamine administration, with levels increasing to 7.38, 9.64 and 7.75 μg L^{-1}. Considering the lower tryptase threshold level suggested by these authors, these increases can be considered as allergic reactions to protamine. Two other patients in our study exceeded the same tryptase threshold at all time points, including at baseline (patient 1; 8.01, 10.00 and 10.90 μg L^{-1} and patient 2; 11.50, 12.70 and 12.30 μg L^{-1}). Therefore,

these increases can be attributed to protamine administration as well as other potential allergic intraoperative and/or preoperative drugs.

In our study, a decrease in blood pressure was observed during anaesthesia, but hypotension was a frequent clinical finding after protamine administration was initiated. However, we did not determine it was an allergic reaction. A concomitant decrease in HR was another common clinical finding during protamine administration in our study.

Not all of the clinical criteria indicative of anaphylaxis can be assessed in this population because of the use of anaesthesia and surgical drapes. For this reason and reasons related to the cardiac bypass procedure, the diagnosis of severe allergic reactions is more difficult in this study population than in regular allergy patients and may require specific practical guidelines. On the other hand, interventions that can change metabolic parameters and acid–base deterioration may cause additional deterioration of myocardial function in patients with compromised cardiac function. Dobutamine and norepinephrine administration might be needed because these agents are necessary to treat changes in cardiac function resulting from the bypass procedure. Therefore, on clinical assessment following treatment of hypotension only the need for epinephrine to improve hypotension may indicate a clinical diagnosis of a severe allergic reaction in this study.

CONCLUSION

1. Although tryptase levels increased significantly when compared with baseline levels, protamine-associated increases were not significant and failed to provide an unequivocal indication of an allergic response to protamine. However, with regard to diagnostic tests, serial measurements of total tryptase which can increase with a sequential decrease in mature β-tryptase during cardiac surgery need to be considered in future studies for confirming a clinical diagnosis of anaphylaxis.

2. The study has several limitations. The interpretation of the tryptase test is slightly confusing because of its different cut-off points and thresholds for allergic reactions. The sample size of our study was small, and there was a low incidence of allergic reactions. In fact, cardiovascular surgery cases can differ from immunological cases in terms of intraoperative procedures, potential allergic drugs used and pathophysiological changes. Additionally, use of anaesthesia and surgical drapes in these patients can mask some of the clinical criteria used in the diagnosis of allergic reactions.

Contributors:

Menekse Oksar – visualization, writing – original draft, resources, investigation;

Hasibe G. Baytan – visualization, writing – original draft, resources, investigation;

Selim Turhanoglu – writing – original draft, resources, investigation;

Tayfun Aybek – writing – review & editing;

Nazife Y. Ardicoglu – project administration, methodology, conceptualization, writing – review & editing;

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