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PENGARUH LAMA KEMATIAN TERHADAP EKSPRESI β -TRYPTASE DAN CHYMASE SEL MAST JANTUNG ANAFILAKTIK

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ABSTRACT

Background: The effects of post mortem interval on tryptase levels are unclear and have been challenging to quantify due to limited and at times contradictory research. **Purpose:** Analyze the effects of Post Mortem Interval (PMI) due to anaphylactic shock on the expression of β -tryptase and mast cell chymase in the heart organ. **Method:** This type of research was an experimental study with a randomized block design (RBD) with the same subjects and a time series for 24 hours, using 5 (five) rabbits. The measurement of β -tryptase and chymase expression was based on immunohistochemical IRS (immunoreactive score) in the heart organs of rabbits experiencing anaphylactic shock sensitization and induction of anaphylactic shock using ovalbumin. **Result:** Based on the results of statistical tests using univariate analysis, there was a relationship between the length of death (post mortem interval) and the expression of mast cells β -Tryptase and cardiac chymase (p -value = 0.006) and chymase (p -value = 0.002) with (p -value < 0.05). The effective test time with β -tryptase markers using cardiac organs was prone to long death time of 0 - 15 hours. The effective check-up time with chymase markers using the heart organ was at a long time of death of 9 hours. **Conclusion:** The results of the study showed that tryptase and chymase could be used as markers of anaphylactic shock.

ABSTRAK

Latar belakang: Efek interval post mortem pada tingkat tryptase tidak jelas dan menantang untuk diukur, karena penelitian yang terbatas dan terkadang kontradiktif. **Tujuan:** Menganalisis pengaruh lama kematian *Post Mortem Interval* (PMI) akibat syok anafilatik terhadap ekspresi β -tryptase dan chymase sel mast pada organ jantung. **Metode:** Jenis penelitian ini adalah penelitian eksperimental dengan Rancangan Acak Kelompok (RAK) dengan sama subyek selang waktu (*time series*) selama 24 jam, menggunakan 5 (lima) ekor kelinci. Pengukuran ekspresi β -Tryptase dan chymase berdasarkan *immunoreactive score* (IRS) imunohistokimia pada organ jantung kelinci yang mengalami syok anafilatik sensitisasi dan induksi syok anafilatik menggunakan ovalbumin. **Hasil:** Berdasarkan hasil uji statistik analisis *univariate* terdapat hubungan antara lama kematian dengan hasil ekspresi sel mast β -Tryptase dan chymase jantung (p -value=0,006) dan chymase (p -value = 0,002) dengan (p -value<0,05). Waktu pemeriksaan efektif dengan penanda β -tryptase menggunakan organ jantung adalah pada rentan waktu lama kematian 0 - 15 jam. Waktu pemeriksaan efektif dengan penanda chymase menggunakan organ jantung adalah pada rentan waktu lama kematian 9 jam. **Kesimpulan:** Hasil penelitian ini menunjukkan bahwa tryptase dan chymase dapat digunakan sebagai penanda terjadinya syok anafilatik.

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INTRODUCTION

Anaphylactic shock is an allergic reaction that appears suddenly, systemic, and life-threatening. The diagnosis of sudden death due to anaphylactic shock is quite difficult and there is no standard post-mortem diagnosis procedure that has been agreed upon in cases of death due to anaphylactic shock. It is caused by a hypersensitivity response mediated by Immunoglobulin E (type I hypersensitivity) caused by an antigen-antibody reaction that occurs immediately after a sensitive antigen enters the circulation (Rengganis, 2016).

Mast cells are abundant in the connective tissue beneath the epithelial surface, including in the submucosal tissues of the gastrointestinal tract, respiratory tract, and in the dermis of the skin. Tryptase, chymase, cathepsin G, and carboxypeptidase are proteases that can be stored in the cytoplasm outside the granules (prepackaged granules) that activate metalloproteases in the extracellular matrix (ECM). Metalloprotease activation damages ECM proteins and induces a remodeling effect on the connective tissue (Rauter *et al.*, 2008).

Mast cell activation is triggered by several pathways. Classically, aggregation of FcεR1 by allergen and IgE triggers release of the preformed mediators by degranulation and of newly synthesized lipids, such as PGD₂ and leukotriene C₄, cytokines such as IL-5, IL-6, IL-8, IL-13, TNF-α, and GM-CSF and chemokines such as MIP-1α, MIP-1β, and MCP-1 (Florholmen *et al.*, 2011; Akdis *et al.*, 2020; Bankova and Barrett, 2019). Through TLRs (Kulka *et al.*, 2004; Kawai and Akira, 2009), the C5aR (CD88) (Bujko *et al.*, 2017) and through FcγRIIa (Zhao *et al.*, 2006) may also activate human mast-cells to release such mediators.

Post-mortem tryptase has been used to aid the diagnosis of fatal anaphylaxis since the 1990s, but it is limited by multiple post-mortem factors. This review aims to investigate the use and interpretation of tryptase, a commonly used biomarker for anaphylaxis, in the post-mortem setting for investigating suspected fatal anaphylaxis (Garland *et al.*, 2020). The role of a forensic expert is urgently needed in various criminal incidents involving the human body, health and life which cannot be easily known by law enforcers. The expert can identify corpses, parts of the human body, condition of bodies, time of death, cause of death to make various written statements. The expert referred here is a forensic expert or judicial medical expert (Idries *et al.*, 2014). The incidence of anaphylactic shock is increasing every year. Epidemiological data show a frequency of 50 - 2000 episodes per 100.000 patients (0.05% -2%) (Simons *et al.*, 2011). The incidence of anaphylactic shock in animals is not yet known (Shmuel and Cortes, 2013). Several incidents of anaphylactic shock that have been reported include dogs (Bosmans *et al.*, 2014) and cattle (Omid, 2009) due to administration of antibiotics.

Histamine is the main product that is produced in anaphylactic shock, but it will be degraded along with post-mortem cytolytic due to protease activity.

The markers such as β-tryptase, chymase, and carboxypeptidase A in immunological examinations are used to determine anaphylactic shock as a cause of death both qualitatively and quantitatively (Tsokos, 2005). The diagnosis of post-mortem anaphylactic shock is a challenge for pathologists today. Methods for examining post-mortem anaphylactic shock using several mediators that play a role in anaphylactic shock are still being developed in various conditions.

MATERIAL AND METHOD

The study was conducted at the Veterinary Pathology Laboratory, Faculty of Veterinary Medicine, Universitas Airlangga in September 2018. The ethical clearance was obtained from Animal Care and Use Committee (ACUC) (Number: 2.KE.157.08.2019). Samples were taken from the sensitized rabbits' heart organ. Five rabbits (*Oryctolagus cuniculus*) used in this study were male adult rabbits aged 6-8 months. The adaptation period was carried out for 1 week. Rabbits were fed on the form of pellets and given drinking water ad libitum that was available at all times. The drinking water in the bottle was always checked and refilled if the water in the bottle was less than half. Provision of more than one source of food and drinking water was also conducted to reduce the possibility of competition and aggressiveness of rabbits (Rommers *et al.*, 2014).

Clinical pathological examination of the complete blood picture of rabbits was carried out to determine the presence of infection or other clinical manifestations that could interfere with the results of the study. Sensitization modified from Shibamoto (2005), rabbits were injected with Freund's Adjuvant (0.5 ml) + 1 mg Ovalbumin (Grade V, Sigma) which had been suspended in 0.5 ml Physiological NaCl intravenously and orally (lavage) 0.5 ml (Shibamoto *et al.*, 2005). The injection was carried out once followed by injection of the antihistamine chlor tri meton orally at a dose of 2 mg/time a total of twice a day on the first day to avoid over-reactions at the first sensitization. After 14 days, the rabbits were re-injected 1 ml ovalbumin suspension intravenously to create anaphylactic shock.

Sampling of rabbit organs was carried out on the 14th day after sensitization. Rabbits were euthanized using pentobarbital sodium, then necropsy was performed to take the heart organs. After that, the organs were immediately placed in a sample pot containing 10% neutral buffered formalin for histopathological preparations and immunohistochemical staining. The number of immunoreactive mast cell in each sample was assessed quantitatively at five Fields of View (LP) at 400x magnification. All of these examinations used immunohistochemistry, counted, and summed on mast cells, which were immunoreactive (positive expressive), in 5 microscope fields of view, with 400x magnification, digital microscope camera connected to micro camera software, which could be evaluated on a computer or a laptop visual monitor.

RESULT

Cardiac tryptase expression

About cardiac tryptase expression, the author analyzed the data using a univariate analysis test which can be seen in Table 1. The univariate analysis showed that there were differences between treatment groups with a significance of $p = 0.006$ ($p\text{-value} < 0.05$) with a confidence level of 95%. Interactions between treatment groups with different PMIs were also shown in the profile of the interaction test plots of the treatment groups with different PMIs (Figure 1). The difference test between subjects/ pairwise comparison was also carried out to find out the differences in mast cell tryptase results between PMIs which showed differences with P provisions. In Figure 1, consists of two assessments X line denoting death for every treatment, counted in hours and Y denoting positive total score.

Table 1. Results of univariate analysis of cardiac mast tryptase cells

	Contrast	Error
Sum of squares	8.243	.106
df	1	2
Mean square	8.243	.053
F	154.864	
Sig.	.006	
Partial eta squared	.987	

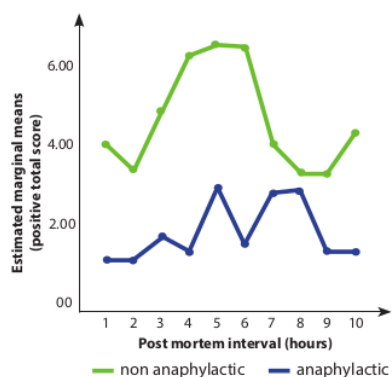


Figure 1. Interaction curves mast cell tryptase between treatment anaphylactic groups and non anaphilactic groups

At PMI 0 or 0 hours of death in the treatment group, it was shown that the quality of the positive immunoreactive tryptase results in the heart was different in the non-anaphylactic and anaphylactic groups. Red arrows indicate negative immunoreactivity in the myocardium, yellow arrows indicated cells mast. The anaphylactic group showed positive immunoreactivity on mast cells and myocardium in Figure 2(a).

PMI 1 or 1 hour long death in the treatment group showed a positive quality of immunoreactive tryptase results in different hearts in the non-anaphylactic and

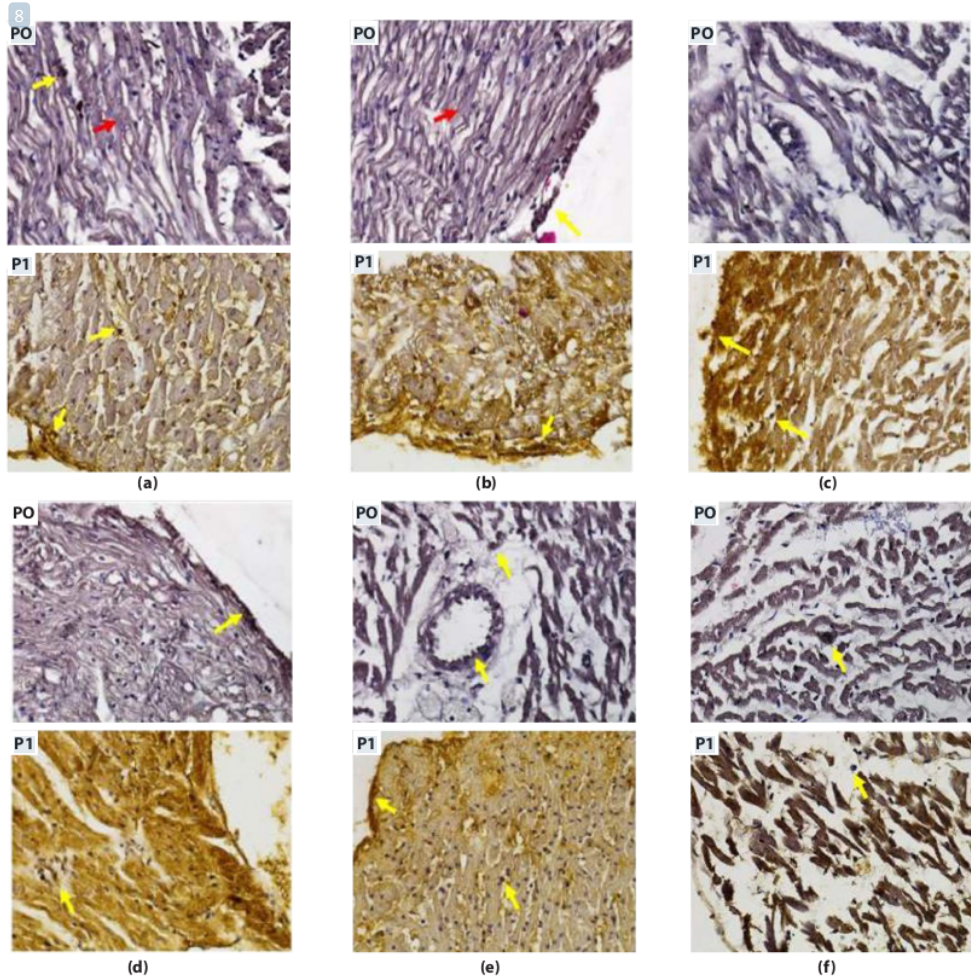
anaphylactic groups. Weak immunoreactive expression of tryptase was observed in the myocardium. Red arrows indicated negative immunoreactivity in the myocardium, yellow arrows indicated mast cells. The anaphylactic group showed positive immunoreactivity on pericardial mast cells Figure 2(b).

PMI 3 or 3 hours of death in the treatment group showed a different quality of positive tryptase immunoreactive results in the heart which was different in the non-anaphylactic and anaphylactic groups. Weak immunoreactive expression of tryptase could also be observed in the myocardium. Yellow arrows indicated mast cells. The anaphylactic group showed positive immunoreactivity on mast cells, myocardium and pericardium in Figure 2(c).

At PMI 6 or 6 hours of death, the treatment group showed a different quality of positive tryptase immunoreactive results in the heart which was different in the non-anaphylactic and anaphylactic groups. Weak immunoreactive expression of tryptase could also be observed in the myocardium. Yellow arrows indicated mast cells. The anaphylactic group showed positive immunoreactivity on mast cells and myocardium. The endothelium appeared positive. Mast cells in the anaphylactic group experienced proliferation in Figure 2(d).

At PMI 12 or 12 hours of death, the treatment group showed a positive quality of immunoreactive tryptase results in a different heart in the non-anaphylactic and anaphylactic groups. In the non-anaphylactic group, tryptase expression was observed in the arterial endothelium. In the anaphylactic group, weak tryptase immunoreactive expression was also observed in the myocardium. The endothelial and vascular muscles also appeared expressive. Yellow arrows indicated mast cells. In the non-anaphylactic group, the connective tissue began to loosen, and the distance between the muscle vesicles widened. Weak positive immunoreactive results were demonstrated in the vascular endothelium. The anaphylactic group showed positive immunoreactivity on mast cells, myocardium and pericardium in Figure 2(e).

At PMI 24 or 24 hours of death, the treatment group showed a positive quality of immunoreactive tryptase results in the heart which was different in the non-anaphylactic and anaphylactic groups. In the non-anaphylactic group, the muscles appeared vacuolated. The distance between the heart muscles also widened. Mast cells could be found in the pericardium. In the anaphylactic group, moderate immunoreactive expression of tryptase was also observed in the myocardium; endothelial and vascular muscles also appeared to be expressive. Strong expression was shown in the pericardium. Yellow arrows indicated mast cells. The anaphylactic group showed strong positive immunoreactivity in the myocardium. The distance between the myocardial muscle vesicles widened. The number of cells in the interstitial tissue was getting scarce in Figure 2(f).



→ Red arrows indicate negative immunoreactivity in the myocardium; → Yellow arrows indicated mast cells

Figure 2. Immunohistochemical staining of mast cell tryptase at (a) PMI 0 hours; (b) PMI 1 hours; (c) PMI 3 hours; (d) PMI 6 hours; (e) PMI 12 hours; (f) PMI 24 hours (Mast cell tryptase cardiac magnification 400x)

Cardiac chymase expression

Based on the multivariate analysis test as a whole (Table 2), it could not be raised but the univariate analysis showed differences between treatment groups with a significance $p = 0.002$ ($p\text{-value} < 0.05$). At PMI 0 or 0 hours of death in the treatment group, it was shown that the quality of the positive immunoreactive chymase results in the heart was different in the non-anaphylactic and anaphylactic groups. Red arrows indicated negative immunoreactivity in the myocardium. Yellow arrows indicated mast cells. The anaphylactic group showed positive immunoreactivity on mast cells, pericardium and myocardium in Figure 3(a).

At PMI 1 or 1 hours of death in the treatment group, it was shown that the quality of the positive immunoreactive chymase results in the heart was different in the non-

anaphylactic and anaphylactic groups. Red arrows indicated negative immunoreactivity in the coronary arteries, yellow arrows indicated mast cells. The anaphylactic group showed positive immunoreactivity in Figure 3(b).

Table 2. Results of univariate analysis of cardiac mast chymase cells

	Contrast	Error
Sum of squares	8.335	.032
df	1	2
Mean square	8.335	.016
F	514.460	
Sig.	.002	

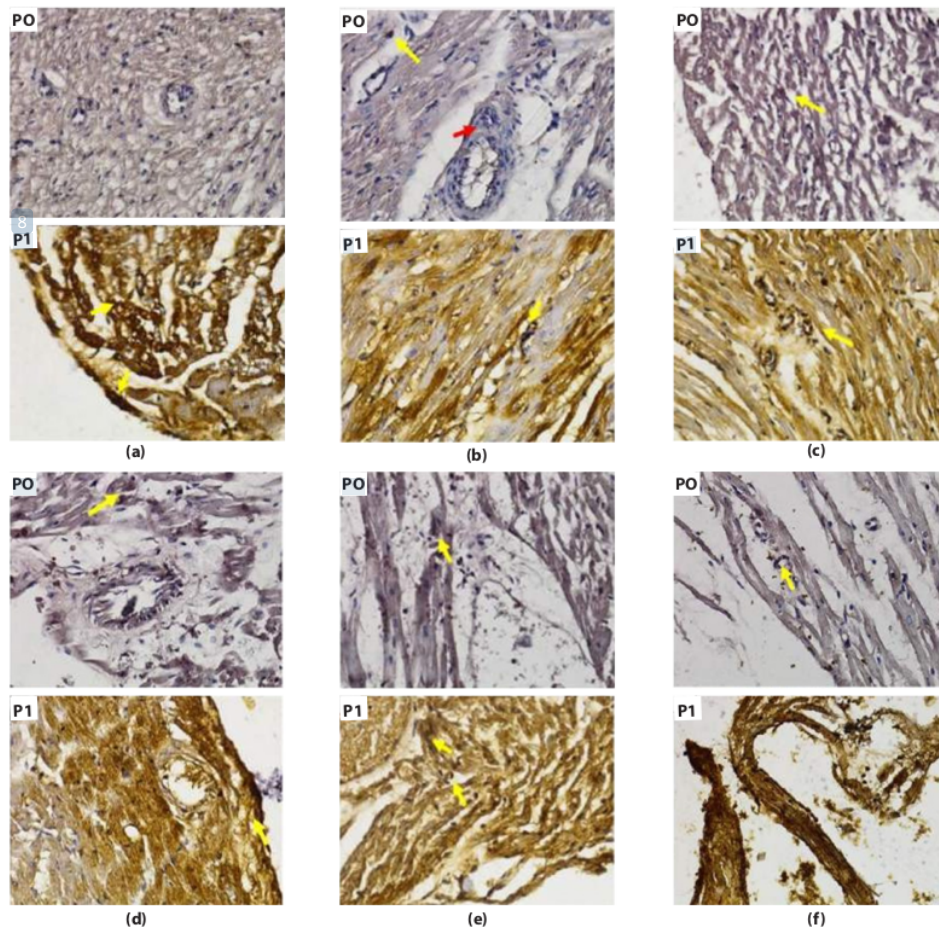
At PMI 3 or 3 hours of death in the treatment group, it was shown that the quality of the positive immunoreactive chymase results in the heart was different in the non-anaphylactic and anaphylactic groups. Yellow arrows indicated mast cells. The anaphylactic group showed positive immunoreactivity on mast cells, myocardium and pericardium in Figure 3(c).

At PMI 6 or 6 hours of death in the treatment group, it was shown that the quality of the positive immunoreactive chymase results in the heart was different in the non-anaphylactic and anaphylactic groups. Yellow arrows indicated mast cells. The anaphylactic group showed positive immunoreactivity on mast cells and myocardium. The endothelium appeared positive in Figure 3(d).

At PMI 12 or 12 hours of death in the treatment group, it was shown that the quality of the positive immunoreactive chymase results in the heart was different in the non-anaphylactic and anaphylactic groups. Yellow arrows indicated mast cells. In the non-

anaphylactic group, the connective tissue began to loosen, and the distance between the muscle vesicles widened. Weak positive immunoreactive results were demonstrated in the vascular endothelium. The anaphylactic group showed positive immunoreactivity on mast cells, myocardium and pericardium in Figure 3(e).

At PMI 24 or 24 hours of death, the treatment group showed a positive quality of immunoreactive chymase results in the heart which was different in the non-anaphylactic and anaphylactic groups. Yellow arrows indicated mast cells. The anaphylactic group showed strong positive immunoreactivity in the pericardium. The distance between the myocardial muscle vesicles widened and many cardiac muscle vesicles underwent lysis/ myolysis. Cell counts in the interstitial tissue were becoming scarce. In the non-anaphylactic group, the muscles appeared vacuolated in Figure 3(f). The distance between the heart muscles also widened. In the anaphylactic group, strong expression was shown in the pericardium with very minimal cellular structure.



→ Red arrows indicate negative immunoreactivity in the myocardium; → Yellow arrows indicated mast cells

Figure 3. Immunohistochemical staining of mast cell chymase at (a) PMI 0 hours; (b) PMI 1 hours; (c) PMI 3 hours; (d) PMI 6 hours (Heart chymase mast cell 400x magnification); (e) PMI 12 hours; (f) PMI 24 hours (Mast cell chymase cardiac magnification 400x)

DISCUSSION

11 Univariate test results of tryptase immunoreactive mast cells in the heart showed differences in the number of expressive mast cells up to 24 hours after death. These results indicated that the examination of cardiac tryptase mast cells could be performed before 24 hours after death. Descriptive immunohistochemical imaging of the heart showed tryptase expression in the myocardium, pericardium and perivascular interstitial connective tissue. Mast cell expression was evident in death before 12 hours in mast cells and heart muscle, but in death after 12 hours tryptase expression was abundant in heart muscle. This could be due to the process of post-mortem autolysis in cardiac mast cells.

Tryptase can spread degranulation signals from activated mast cells to other mast cells (Amin, 2012). Serum tryptase peaks between 60 - 90 minutes after the onset of anaphylactic symptoms and remains elevated for up to 5 hours depending on the severity of the anaphylaxis, which makes tryptase an effective marker in anaphylactic shock test. This explanation indicates that the tryptase examination can be carried out more than 5 hours up to 15 hours in the lungs. Tryptase is a type of water-soluble (hydrophilic) protein enzyme (esterase protein) with a molecular weight of 110 - 130 kDa. Tryptase binds to heparin or other proteoglycans on the sides of the cationic groove. Tryptase tetramer bound to heparin is stored in mast cell cytoplasmic granules (Fu *et al.*, 2019). In small quantities, tryptase is found in basophils. Tryptase is degranulated in the form of complex proteoglycans with a molecular weight of 200 - 250 kDa. Tryptase in the form of a proteoglycan complex is localized and does not diffuse beyond its activation site. However, systemic tryptase levels will increase only in massive mast cell activation causing anaphylactic shock or mastocytosis.

The univariate test results of immunoreactive chymase mast cells in the heart showed differences in the number of expressive mast cells up to 18 hours after death. These results indicated that the examination of cardiac tryptase mast cells could be performed before 18 hours after death. Descriptive immunohistochemical imaging of the heart showed chymase expression in the myocardium, pericardium, and perivascular interstitial connective tissue. Mast cell expression was evident in death before 12 hours in mast cells and heart muscle, but in death after 12 hours tryptase expression was abundant in heart muscle. This could be due to the process of post-mortem autolysis in cardiac mast cells.

In the non-anaphylactic group, both tryptase and chymase showed a difference in the number of expressive mast cells with lower quality of expression than the anaphylactic group. Tryptase and chymase

expression in the non-anaphylactic group occurred due to the exposure to homogenous and aerogenous antigens during treatment that could cause the release of IgE resulting in tryptase and mast cell chymase degranulation. In the non-anaphylactic group, the elevation of tryptase and chymase did not occur drastically due to excess production of IgE, so that histamine was not degranulated rapidly.

The above description showed that tryptase and chymase could be used as markers of anaphylactic (non-anaphylactoid) shock in the heart with different numbers and qualities of chymase and tryptase mast cell expression. In the case of investigations to assist experts in carrying out tests and based on the results of the research above, it is necessary to make test standards/cut offs. The effective test time with β -tryptase markers using cardiac organs is prone to long death time of 0 - 15 hours. The effective check-up time with chymase markers using the heart organ was at a long time of death of 9 hours.

In human case, the effects of post-mortem interval on tryptase levels were unclear and have been challenging to quantify, due to limited and at times contradictory research. A 2013 paper by Donaldson *et al.* found that increased post-mortem interval was associated with increased post mortem tryptase (Donaldson *et al.*, 2013). Another study discovered a minor increase in post-mortem tryptase levels as post-mortem interval increased, with a median increase from 6mg/L at death to 8.8 mg/L two days after death (Woydt *et al.*, 2018). This increase was enough to exceed the proposed post-mortem cutoff for anaphylaxis of 44.3 mg/L in only one out of 80 samples, whilst two cases actually showed decreases in tryptase with longer post-mortem interval (Woydt *et al.*, 2018). Interestingly, two cases reports, demonstrated a decrease in serial post-mortem tryptase levels over a longer time period than that investigated by Woydt *et al.* (2018) and in cases of anaphylactic death (Sravan *et al.*, 2015). Sravan *et al.* (2015) and Tse *et al.* (2018) showed a decrease in post mortem tryptase from 522mg/L (3 days post death) to 300mg/L (6 days post death) and 130 ug/L (2 days post death) to 84.4 ug/L (3 days post death), respectively.

Post-mortem processes may increase or decrease in tryptase levels. Post-mortem cytolysis and associated degranulation of mast cells containing tryptase may explain a possible increase in tryptase as post-mortem interval increases (Tse *et al.* 2018). Tryptase degradation and post-mortem clearance may explain decreasing tryptase. The measurement of serum mast cell-specific chymase levels might be an additional method for post-mortem diagnosis of anaphylaxis (Nishio *et al.*, 2005).

CONCLUSION

Based on the results of statistical tests using univariate analysis, there was a relationship between the length of death *Post Mortem Interval* (PMI) and the expression of β -Tryptase and chymase mast cells, indicated by differences in the number of immunoreactive mast cells, namely β -tryptase in the heart (p -value = 0.006) and chymase in the heart (p -value = 0.002) with (p -value < 0.05) rabbit (*Oryctolagus cuniculus*) experiencing anaphylactic shock. The effective test time with β -tryptase markers using cardiac organs was prone to long death time of 0 - 15 hours. The effective check-up time with chymase markers using the heart organ was at a long time of death of 9 hours.

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