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Effects of Suture Implantation Using Different Suture Materials on the Skin Histopathology, Immune Expression of Interleukin-6, and Hematological Parameters in Rat

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ABSTRACT

Suture implantation is a procedure to promote rearrangement of the extracellular matrix. Various cellular responses of post-suture implantation affect the outcome of this procedure. The current study aimed to analyze the effects of suture implantation using polycaprolactone/polylactic acid/hyaluronic acid (PCL/PLA/HA) on skin histopathology, expression of IL-6, and hematological parameters in rat models. To conduct the study, 25 male Sprague Dawley rats, three months old were randomly divided into five groups, including G1 (control), G2 (sham, group injected using skin cannula), and G3-G5 (suture implanted groups). For the suture-implanted groups, a cannula was used using suture materials. Specifically, G3 received truglyde implants, G4 received PCL/PLA/HA implants, and G5 received polydioxanone (PDO) implants. The back skin and blood samples were collected on day 3. Histopathological analysis was conducted on the samples using H and E, Congo red, immunohistochemistry against IL-6, and hematology. The analysis of the data revealed that the group with suture implantation using PCL/PLA/HA had the smallest wound area, compared to the other implanted groups. Further, the PCL/PLA/HA group showed a significant decrease in eosinophils infiltration and IL-6 level on the skin samples after suture implantation. Moreover, there were no significant differences across the groups in most of the hematological parameters after suture implantation, including total erythrocytes, hemoglobin, eosinophil, basophil, and monocyte levels. The total neutrophils increased after suture implantation in all groups, while the total lymphocytes decreased. It can be concluded that the best material according to parameters evaluated in the current study for suture implantation was PCL/PLA/HA.

Keywords: Eosinophil, Histopathology, Hyaluronic Acid, Interleukin-6, Polycaprolactone, Polylactic Acid, Suture implantation

INTRODUCTION

Suture implantation in the skin tissue is a common procedure in cosmetic surgery, known to promote the rearrangement of the collagen of an extracellular matrix (Wang et al., 2023). The rearrangement of the extracellular matrix is expected to increase collagen deposition and repair tissue during the mechanism of aging (Adelman and Cornwell, 2020). Synthetic polymers have been developed for suture implantation, offering the ability to modulate tissue characteristics by promoting interactions between cells and the matrix, as well as facilitating revascularization (Cornwell et al., 2016). However, it is important to note that the diverse cellular responses elicited post-suture implantation can significantly influence the overall outcome of the procedure (Lovric et al., 2018).

A common cellular response following implantation is an increase in inflammation which is predominantly caused by eosinophils due to a hypersensitivity mechanism (Aronson et al., 2022). Eosinophils play significant roles in skin homeostasis and the regulation of T helper 1 (Th1) and Th2 balance. However, the excessive increase in eosinophils causes massive local inflammation, prolongs the duration of inflammation, and inhibits the process of tissue wound healing (Blanchard and Rothenberg, 2009). Moreover, eosinophil promotes a synthesis of pro-inflammatory cytokines, such as interleukin-6 (IL-6, Li et al., 2022). Interleukin-6 is essential during an acute inflammatory phase in wound healing; however, it must be decreased in the late processes to increase the matrix collagen deposition (Johnson et al., 2020). The suture material significantly affects the skin matrix rearrangement after suture implantation. A good suture material must be well tolerated by the skin with minimum inflammatory responses. Therefore, it is essential to develop suture materials for implantation using compounds that are well-tolerated by skin tissue, prevent delayed wound healing, and enhance clinical outcomes.

Polylactic acid (PLA) is a resorbable thermoplastic polyester compound, which is used in bone surgery because of its bio-resorbability and biocompatibility (Li et al., 2020). Hyaluronic acid (HA) is a component that can stimulate tissue

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adhesion after implantation (Corduff et al., 2021). Polylactic acid is commonly combined with HA and known as PLA/HA (Åkerlund et al., 2022), which is regularly used to increase tissue toughness and improve the tissue's mechanical properties. However, PLA/HA can be degraded in a short period after implantation and makes poor clinical responses. Hence, it can be combined with polycaprolactone (PCL) which is a bioresorbable polyester used in cosmetic surgery to improve matrix deposition. Although PCL is frequently utilized in bone applications, its use as an implantation material on the skin remains relatively unexplored (Ng et al., 2007). The present study aimed to analyze the effects of the implantation of different suture materials on skin histopathology, expression of IL-6, and hematological parameters in male rats.

MATERIALS AND METHODS

Ethical approval

The animal experimentation was approved by the ethical clearance committee from Lembaga Penelitian Universitas YARSI, Jakarta with registration number 134/KEP-UY/EA.10/VI/2023. This study was conducted from July until December 2023 in the Laboratory of Animal Models IratCo, Bogor, Indonesia.

Study design

This study involved 25 male Sprague Dawley rats (Laboratory of Animal Models IratCo, Bogor), weighing 250 grams, and aged 3 months old. The rats were housed in acrylic cages with access to water and feed *ad libitum*. The rats were randomly divided into five groups, including a control group without induction (G1), a sham-induced using cannula without suture implant (G2), suture implanted groups (G3-G5), while third group was implanted using truglyde (G3), fourth group was implanted using PCL/PLA/HA (G4), and fifth group was implanted using polydioxanone PDO (G5).

Before the suture implantation, the rat was intraperitoneally anesthetized using ketamine (10 mg/kg BW) in combination with xylazine (2 mg/kg BW, Sotoudeh and Namavar, 2022). The hair on the lateral side of the vertebrae was shaved using a clipper (Indonesia) and the area was disinfected using isopropyl alcohol. Subsequently, the cannula (Dermax, China) was implanted into the dermal part of the rat skin, as per the method outlined by Janhofer et al. (2018). The cannula (Nanumcompany, South Korea), truglyde (Truglyde, India), PCL/PLA/HA (APTOS, Georgia), and PDO (Whitemedience, South Korea) were used in this study. The suture was implanted as long as 2 cm on the lateral side of the rat vertebrae.

Sample collection

The rats were maintained for 3 days. On day 3, the rats were anesthetized by ketamine and xylazine using similar doses to the suture implantation procedure. After that, the rats' blood samples (1 ml) were collected from the retro-orbital plexus and stored using an EDTA tube (1 mL). Finally, they were euthanized using cervical dislocation. The skin samples were then collected and fixed using 10% neutral buffer formalin.

Laboratory tests

The blood samples were tested against several hematological parameters, including total erythrocytes, leucocytes, platelets, neutrophils, eosinophils, basophils, lymphocytes, and monocytes, and the level of hemoglobin. The blood samples were tested using an automated haemo-analyser (VetScan VS2, USA).

The skin samples were dehydrated using graded alcohol, and xylene and blocked using liquid paraffin. The samples were cut using a microtome. The skin slides were then stained by hematoxylin and eosin (H and E, Feldman and Wolfe, 2014), Congo red staining (Song et al., 2018), and immunohistochemistry (IHC) against antibody anti-IL-6 (Prakoso et al., 2020). The slide was dehydrated and applied with endogenous peroxidase and protein block. The slide was then incubated using antibody anti-IL-6 (Novocastra, USA) for 30 minutes. The slide was incubated using post-primary antibody and diethylaminobenzidine (DAB). The slide was counter-stained using hematoxylin and mounted using Entelan nue. The slides were then photographed using an Olympus microscope (CX33, Japan) at 400× magnification and analyzed using ImageJ software (NIH, USA). The H and E slide was applied regarding the wound tissue area, the Congo red for the number of eosinophils, and the IHC of IL-6 for the density of immunoreactivity of IL-6 were conducted.

Data analysis

The collected data was analyzed statistically using SPPS 26. The normality test was performed using the Shapiro-Wilk test. The normally distributed and homogenously data, especially hematological parameters were analyzed using parametric analysis. The parametric analysis was the analysis of variance (ANOVA) followed by a post hoc test using the least significant difference (LSD). In contrast, the Congo red and IHC IL-6 data were analyzed using the Kruskal Wallis and Mann Whitney-U test. The significance value used in this study was 0.05 and the data were presented as mean and standard of deviation.

RESULTS AND DISCUSSION

The results indicated that the group implanted using PCL/PLA/HA had the smallest area of inflammation, compared to the other groups on day 3 ($p < 0.05$). This was followed by the groups using PDO and truglyde concomitantly. While the average number of eosinophils increased in the truglyde group, it decreased in the group using PDO and PCL/PLA/HA implants, compared to the truglyde group ($p < 0.05$). These findings were consistent with the immunoreactivity of IL-6 on the skin after suture implantation, which increased after implantation. The highest IL-6 expression was determined in the group truglyde. However, the minimum immune expression of IL-6 was PCL/PLA/HA ($p < 0.05$, Table 1).

There were no significant differences in several hematological parameters after suture implantation, including total erythrocytes, hemoglobin level, eosinophils, basophils, and monocytes ($p > 0.05$). The findings revealed that the total leucocytes and platelets increased in the truglyde and PDO groups, compared to others ($p < 0.05$). The total neutrophil count increased following the implantation of suture materials in all groups ($p > 0.05$). The neutrophils significantly increased in group truglyde, PCL/PLA/HA, and PDO, with no significant difference among the groups ($p > 0.05$). In contrast, the total lymphocytes indicated a trend of decreasing after suture implantation using truglyde, PCL/PLA/HA, and PDO ($p < 0.05$, Table 2).

Table 1. Inflammation area, number of eosinophils, and immunoreactivity of IL-6 in the rat skin after suture implantation

Parameter	Group (mean ± standard deviation)				
	G1 (Control)	**G2 (Sham)**	**G3 (Truglyde)**	**G4 (PCL/PLA/HA)**	**G5 (PDO)**
Wound tissue area	0.00 ± 0.00	0.00 ± 0.00	14.32 ± 4.24a	6.14 ± 4.00b	14.32 ± 4.24a
Number of eosinophils	0.30 ± 0.65	0.73 ± 0.86	18.00 ± 14.95a	4.20 ± 4.59b	11.10 ± 6.53c
Immunoreactivity of IL-6	0.25 ± 0.59	0.33 ± 0.72	9.25 ± 5.11a	0.74 ± 1.16b	1.94 ± 2.29c

[abc] different superscript indicated significant differences ($p < 0.05$). A control group without induction (G1), a sham-induced using cannula without suture implant (G2), suture implanted groups (G3-G5), while third group was implanted using truglyde (G3), fourth group was implanted using PCL/PLA/HA (G4), and fifth group was implanted using polydioxanone PDO (G5).

Table 2. Haematological profile of rat models after suture implantation

Parameter	Group (mean ± standard deviation)				
	G1 (Control)	**G2 (Sham)**	**G3 (Truglyde)**	**G4 (PCL/PLA/HA)**	**G5 (PDO)**
Erythrocytes ($\times 10^6$ mm^3)	7.19 ± 0.64	7.84 ± 0.38	8.05 ± 0.39	7.83 ± 0.70	7.60 ± 0.69
Haemoglobin (g/dL)	12.98 ± 0.81	13.48 ± 0.58	13.68 ± 0.35	13.50 ± 0.84	12.93 ± 0.78
Leucocytes ($\times 10^3$ mm^3)	14.93 ± 3.47	14.67 ± 3.39	17.94 ± 2.14a	14.00 ± 3.18	17.75 ± 2.90a
Platelets ($\times 10^3$ mm^3)	790.16 ± 115.84	832.33 ± 122.65	942.20 ± 144.21a	726.00 ± 117.90	930.00 ± 170.27a
Neutrophils ($\times 10^3$ mm^3)	0.24 ± 0.10	0.29 ± 0.67	0.72 ± 0.52a	0.61 ± 0.50a	0.68 ± 0.66a
Eosinophils ($\times 10^3$ mm^3)	0.01 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.02 ± 0.03	0.04 ± 0.04
Basophils ($\times 10^3$ mm^3)	0.04 ± 0.01	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.01	0.02 ± 0.00
Lymphocytes ($\times 10^3$ mm^3)	16.33 ± 3.03	16.38 ± 2.76	14.65 ± 2.64b	10.02 ± 3.50a	13.45 ± 2.32b
Monocytes ($\times 10^3$ mm^3)	1.61 ± 0.45	1.17 ± 1.16	1.71 ± 1.11	1.81 ± 1.30	1.61 ± 0.91

[abc]different superscript indicated significant differences ($p < 0.05$). A control group without induction (G1), a sham-induced using cannula without suture implant (G2), suture implanted groups (G3-G5), while third group was implanted using truglyde (G3), fourth group was implanted using PCL/PLA/HA (G4), and fifth group was implanted using polydioxanone PDO (G5).

The macroscopical signs, and microscopical findings include of histopathology, eosinophils, and immunoreactivity of the skin after suture implantation were shown in Figure 1 in a comprehensive detail.

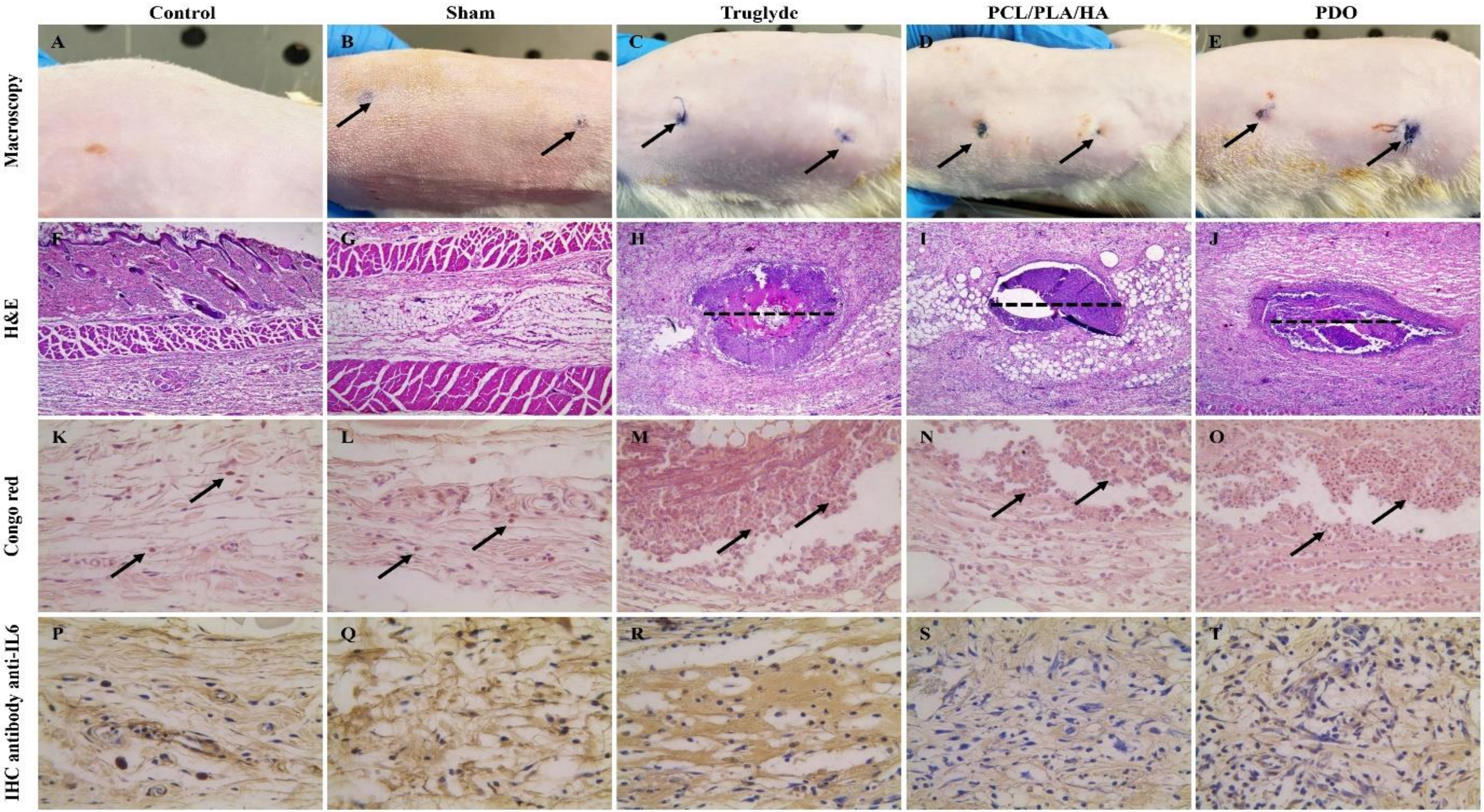

Figure 1. Macroscopy, histopathology, eosinophils, and immunoreactivity in the skin of rat models after suture implantation. There are no macroscopical (A) and microscopical (F) lesions of the skin in a normal rat, the skin also shows a mild expression of eosinophils (arrow; K) and IL-6 (P) in the dermal part; sham group showed the similar pattern to normal group (arrow; B, G, L, Q); however, the truglyde group indicated severe swollen (arrow; C) during the macroscopical examination, large wound area (dotted line; H), severe number of eosinophils (arrow; M), and strong immunoreactivity of IL-6 (brown color) in dermal part (R); the PCL/PLA/HA group showed a swollen (D) in one side of suture implant with a smaller wound area (I), minimum eosinophil numbers (arrow; N), and mild immunoreactivity of IL-6 (browm color; S); PDO group indicated a similar macroscopic lesion (arrow; E) to the PCL/PLA/HA group, but with wider wound area (dotted line; J), moderate eosinophil numbers (arrow; O), and moderate immunoreactivity of IL-6 (brown color; T). H and E, 40× (F-J); Congo red, 400× (K-O); IHC antibody anti-IL-6, 400× (P-T).

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The collagen deposition is expected to increase skin tension and strength. The success of collagen deposition depends on the suture types, site of implantation, and immune status of the patient. However, the suture types become the most eminent factor in matrix deposition (Kim et al., 2019). For several decades, PDO has been the most thread used for suture implantation in aesthetics. The utilization of PDO causes minimum histopathological effects and can be used to correct the nose and cheek shape, nose position, and skin tensile strength (Unal et al., 2021). However, a previous study reported that the utilization of PDO generates barbed sutures, secondary infection, thread palpability, abscess, and chronic pain (Surowiak, 2022). According to Wu (2019), PDO has a limited duration within the skin tissue and may eventually dissolve, resulting in the loss of its potential benefits as a dermal filler and collagen deposition promoter. However, the current study indicated that PDO implantation induced significant skin tissue lesions and triggered an escalation in inflammatory responses within 3 days. The histopathological changes were especially severe infiltration of eosinophils and increased density of immunoreactivity of IL-6.

However, the area of inflammation, eosinophil infiltration, and immunoreactivity of IL-6 in a group using PCL/PLA/HA is lower than in the PDO group. These mechanisms are influenced by the several compounds inside the suture material. Besides PDO, the most common type of suture ingredient consists of PLA/HA. PLA is an inert component that can be used to stimulate the synthesis of collagen (DeStefano et al., 2020). As a biodegradable microparticle, the PLA promotes collagenesis within the dermal part through its potency to activate fibroblast activity (Nethi et al., 2019). Moreover, the potency of PLA as a dermal filler and matrix collagen promoter can be increased with the combination using HA. Hyaluronic acid consists of glycosaminoglycan that can increase skin hydration and collagen expression, especially type 1 collagen (Bartus et al., 2013). The previous study by Zhao et al. (2024) described PLA which is combined with HA potential for dermal filler, especially preventing oedema, swelling, and redness on the skin tissue. Chen et al. (2023) described in their study that a combination of HA and PLA promotes wound healing without hypertrophic scar generation.

In addition, PCL combined with PLA/HA is a new model of suture implant combination. Polycaprolactone is a biopolymer which is essential to increase skin tensile strength and can decrease thermal transition effects post-implantation (Pitjamit et al., 2020). Polycaprolactone is also applicable for hard tissue surgery, such as bone injuries (Dehghani Firoozabadi et al., 2022). The combination of PCL with PLA/HA has been shown to prolong the biodegradation of suture material post-implantation and minimize brittleness (Moura et al., 2019). The decrease in brittleness and biodegradation improves collagen density and also decreases inflammatory responses. This mechanism is marked in the current study by the minimum expression of IL-6 and eosinophils. The minimum of eosinophils in PCL/PLA/HA group indicates that the hypersensitivity and rejection response was lower than the other materials. Furthermore, IL-6 is a pro-inflammatory cytokine, and its expression changes following external insults (Uciechowski and Dempke, 2020). However, the minimum immune expression of IL-6 after suture implantation is essential to increase tissue regeneration and matrix collagen rearrangement (Johnson et al., 2020).

The suture implantation causes a systemic immune response which is marked by a change of leucocyte, neutrophil, and lymphocyte after three days. This is a typical cellular immune response in the body of the host. The leucocytes increase as the first lineage of cellular response (Selvi et al., 2016), additionally, the neutrophil and lymphocytes increase in responding to inflammatory stimulation (Cai et al., 2021) and tissue repair (Prakoso and Kurniasih, 2018), concomitantly.

CONCLUSION

This study revealed that the implantation of suture materials using PCL/PLA/HA has better clinical outcomes regarding wound tissue area, number of eosinophils, and IL-6 during an acute phase of post-implantation. This finding was indicated by the decrease of the wound area, eosinophils infiltration, and immunoreactivity of IL-6, rather than the hematological profile. Therefore, advanced studies regarding the utilization of PCL/PLA/HA against a longer observation period using more complex parameters such as COX-2, CD4+, CD8+, VEGF, and FGF should be conducted to prove its safety and potency as a dermal filler.

DECLARATIONS

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Authors' contributions

Muhammad Hafid Ernanda designed, performed an experiment, data analysis, and drafted of manuscript. Ndaru Anri Damayanti designed monitored, evaluated the data analysis, and revised the draft of the manuscript. Wening Sari performed data analysis and corrected the paper. The last edition of the manuscript was read and approved by all authors.

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Availability of data and materials
The data to support this study finding is available upon reasonable request to the corresponding author.

Competing interests
The authors have no conflict of interests.

Ethical considerations
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