

Effect of Ropivacaine Around the Incision on the Expression of Platelet Protein Derived Growth Factor and Neutrophil Cell Infiltration in the Wound Healing Process (Experimental Laboratory Study on Wi

by Nasrulloh Nasrulloh

Submission date: 19-Apr-2023 01:25PM (UTC+0800)

Submission ID: 2069085541

File name: 04._Effect_of_Ropivacaine.pdf (887.83K)

Word count: 5251

Character count: 27370

13
Effect of Ropivacaine Around the Incision on the Expression of Platelet Protein Derived Growth Factor and Neutrophil Cell Infiltration in the Wound Healing Process (Experimental Laboratory Study on Wistar Rats)

¹Nasrulloh, ¹Hamzah, ¹Arie Utariani, ^{2,3}Imam Susilo*

16
¹Anesthesiology and Reanimation Department, Faculty of Medicine Universitas Airlangga/ Soetomo General Hospital, Surabaya, Indonesia. ²Pathology Anatomy Department, Faculty of Medicine Universitas Airlangga/ Soetomo General Hospital. ³Department of Health Studies Faculty of Vocation Airlangga University Surabaya, Indonesia

*Corresponding author, email: imam-susilo@fk.unair.ac.id

ABSTRACT

Background: The incision wound produces pain. Inadequate postoperative pain management can result in impaired wound healing. One important factor in wound healing is the presence of PDGF growth factors, and also a decrease in the number of neutrophil cells after the end of the first phase of wound healing. PDGF is a growth factor that is believed to be an important factor in any wound healing process; and a rapidly decreasing neutrophil count indicates a better wound healing process. The purpose of this study was to prove the effect of ropivacaine infiltration injection to increase PDGF expression and decrease the number of neutrophil cells in the wound healing process.

Methods: Twenty four male wistar rats were divided into 2 groups and then superficial-thickness incisional wound was made on the back of each rat. The control group was not given ropivacaine infiltration injection, while the treatment group was given. Each group was divided into 2 sub-groups, each consisting of 6 mice, terminated on the 3rd and 7th day. Then a histopathological evaluation was performed to determine whether there was an increase in PDGF expression and a decrease in the number of neutrophil cells around the incision wound tissue. The collected data were then analyzed using the SPSS program.

Results: The administration of ropivacaine infiltration in superficial-thickness incisional wounds improved wound healing characterized by the increase in the number of PDGF expression and the decrease in the number of neutrophil cells

Conclusion: Injection of ropivacaine infiltration around the incision wound has a beneficial effect on the superficial wound healing process of Wistar rats.

Keywords: Neutrophil, PDGF, Ropivacaine, Wound healing



INTRODUCTION

Direct application of local anaesthetic to the wound can block the transmission of pain to nociceptive afferents on the wound surface. Local anaesthetic also inhibit the local inflammatory response in wounds which under normal conditions sensitize nociceptive receptors and result in pain and hyperalgesia.¹ Infiltration of local anaesthetic reduces the release of mediators from neutrophils, reduces adhesion of neutrophils to the endothelium, reduces the formation of free oxygen radicals, and reduces the occurrence of swelling.² Infiltration of local anaesthetic is especially useful in surgeries where visceral pain is less involved, such as inguinal herniotomy surgery where the pain score can be reduced up to 24 hours postoperatively and reduces analgesic use. The use of local anaesthetic infiltration in sectio Caesarean wounds reduces the requirement for morphine at 24 hours postoperatively.³

The local anaesthetic ropivacaine infiltration reduces pain intensity by inhibiting the transmission pathway of pain impulses, thereby decreasing glucocorticoid hormone secretion and eliminating one of the inhibiting factors for wound healing. Research conducted on animals and humans has shown that ropivacaine is less toxic than bupivacaine.⁴

The initial phase of wound healing occurs extravasation of blood components and vasoactive materials. Vascular permeability increases temporarily so that neutrophils (Polymorphonuclear (PMN)), platelets, and plasma proteins can infiltrate the wound. Platelets release several factors, including platelet-derived growth factor (PDGF) and transforming growth factor (TGF), which attract PMN to the injured area. PMN together with macrophages cleaned debris in the wound, releasing growth factors. Then the proliferation phase begins 72 hours after the injury occurs with the presence of fibroblasts that are drawn



to the wound area by growth factors, then collagen formation begins. The remodeling process lasts several months.⁵

The incidence of pain increases the levels of β endorphins secreted by the pituitary gland. This suppresses the macrophages so that their activity decreases. This decrease results in decreased activity of cytokines released by macrophages such as Tumor Necrosis Factor (TNF) α , Interleukin (IL) -1, IL-6, IL-8, TGF β ; So that this hinders wound healing.⁴

Based on data from the United State Institute of Medicine, 80% of patients undergoing surgery reported postoperative pain, with 88% of these patients experiencing moderate, severe, or extreme pain levels.⁶ Data in the Regional General Hospital (RSUD) Dr. Soetomo Surabaya found that most patients (59.2%) experienced moderate-severe postoperative pain in the first 24 hours postoperatively.⁷

Based on these descriptions, researchers are encouraged to conduct research on the effect of ropivacaine infiltration as a local anaesthetic drug through the inhibition process of pain stimulation, on PDGF expression and the number of neutrophil cells which are important factors in the wound healing process.²²

MATERIALS AND METHODS

Research design

This research is a laboratory experimental design with a "randomized post test only control group design" using Wistar rats as research objects. The treatment given was the administration of local anaesthetic bupivacaine infiltration by evaluating the microscopic image of the neutrophil cell count and PDGF protein expression. At the beginning of the



study, control by design was carried out by homogenizing the research sample. Meanwhile, measurements were made only at the end of the study.

Research procedure

The experimental animal was the Wistar rat with an age of 2 to 2.5 months and a weight of 250-300 grams. ⁴⁹ During the experiment, experimental animals were placed in cages and given standard food and adequate drinking.

The selection of mice was carried out by paying attention to inclusion and exclusion criteria, so that 24 rats were selected to be used in the study. The next step is acclimatization, done to give the mice time to adapt to the research environment. Acclimatization is carried out for one week. Acclimatization was carried out by equalizing food, drinks, and measuring the weight of the rats. Mice that have gone through the acclimatization period can be used for research. These mice were then grouped using a simple randomized method, divided into 4 experimental groups. Each group contains 6 rats which are divided into 4 cages with the size of each cage 30x20x7 cm

A total of 24 rats, divided into 4 groups which were randomly assigned to each consisting of 6 rats. In treatment group 1 (P1), Wistar rats were given 2 cm incision wounds and were infiltrated with 0.2% ropivacaine for a total of 1 ml before the incision wound was closed, then evaluated on day 3. In treatment group 2 (P2), Wistar rats were given 2 cm incision wounds and given 0.2% ropivacaine infiltration for a total of 1 ml before the incision wound was closed then evaluated on day 7. In the control group 1 (K1), Wistar rats who were given 2 cm incision wounds without being given ropivacaine infiltration and were not given any injection were then evaluated on day 3. In the control group 2 (K2), Wistar rats that were



given 2 cm incision wounds without being given ropivacaine infiltration and were not given any injection were then evaluated on day 7.

Rats in group P1 and group P2 were sedated using ketamine-xylazine at a dose of 75-100 mg / kg + 5-10 mg / kg via intraperitoneal with a duration of 10-30 minutes. In the treatment group I (P1) rats, after anesthetizing the hair around the back was shaved clean and disinfected using povidone iodine. Subsequently, a 2 cm long slice was made and a depth of up to the subcutaneous. The incision was cleaned and smeared with povidone iodine solution, then the subcutaneous tissue was given 1 ml of 0.2% ropivacaine infiltration around the wound approximately 0.5 cm around the wound, then the wound was treated and covered with sterile tegaderm. In treatment group 2 the same thing was done.

In the first control group (K1), after the rats anesthetized the hair around the back was shaved clean and disinfected using povidone iodine. Subsequently, a 2 cm long slice was made and a depth of up to the subcutaneous. The wounds were cleaned and covered with povidone iodine solution, then covered with sterile tegaderm. The second control group mice also did the same thing.

On day 3 of the group 1 (P1) and 1 (K1) treatment rats, the rats were anesthetized using ketamine. After the rats were sedated, a biopsy excision was performed on the 3 cm square cut scar tissue with a depth of up to the subcutaneous. On day 7, group 2 (P) and control 2 (K2) mice also did the same thing.

The making of histological preparations was carried out at the Department of Pharmacology, Faculty of Medicine, Airlangga University. The procedure for making paraffin blocks and the Haematoxylin Eosin smear was carried out by the standard method.

The procedure for making immunohistochemical preparations was carried out with the anti-



rat PDGF monoclonal antibody. The preparations were rehydrated with 100% ethanol for two minutes, 95% ethanol for two minutes, and 70% ethanol for one minute, then rinsed with H₂O for one minute. The preparations were immersed in room temperature peroxidase blocking solution (PBS) for 10 minutes and incubated in prediluted blocking serum 25 C for 10 minutes. The preparations were immersed in PDGF monoclonal antibody primer for 30 minutes and rinsed with PBS for 5 minutes. Incubation with secondary antibodies for 30 minutes, and rinsed with PBS. The preparation was put into Streptavidin Horseradish Peroxidase (Streptavidin HPS) for 30 minutes, rinsed with PBS. Put it in the chromogen substrate for 5 minutes, rinse PBS, then aquadest. Given Mayer Hematoxylin for 6 minutes and rinsed with running water. Microscopic observations were carried out at the Department of Anatomical Pathology FK UNAIR / RSUD Dr. Soetomo Surabaya.

Statistic analysis

The data collected were processed with statistical software SPSS version 17, then analyzed statistically descriptively in the form of percentages, graph tables or figures. The normality test was performed using the Kolmogorov-Smirnov test. Parametric statistical tests are used if the data curve is normally distributed, if the data curve is oblique, non-parametric statistical tests will be used. Analysis for comparative purposes used statistical analysis of variant (ANOVA). Comparison of the mean number of PDGF and neutrophil expression values between control and treatment groups, the Kruskal-Wallis test was performed.



RESULTS

PDGF expression

On day 3, the results of the calculation of the average number of PDGF expressions in the treatment group (P1) were 7.50, more than the control group (K1) of 6.50. Meanwhile, on day 7, the results of the calculation of the average number of PDGF expressions in the treatment group were 7.00, more when compared to the control group of 6.17.

Based on the results of the research that has been obtained, statistical analysis tests were carried out between the control and treatment groups on the 3rd and 7th day. First, the normality test was carried out in each group using the Kolmogorov-Smirnov test. If the results obtained are $p \text{ value} > \alpha = 0.05$, then the data distribution is normal. On day 3, the control group obtained $p = 0.056$, and the treatment group also obtained $p = 0.056$. Whereas on the 7th day, the control group obtained $p = 0.200$ and the treatment group obtained $p = 0.036$. So it can be concluded that not all data in each group are normally distributed.

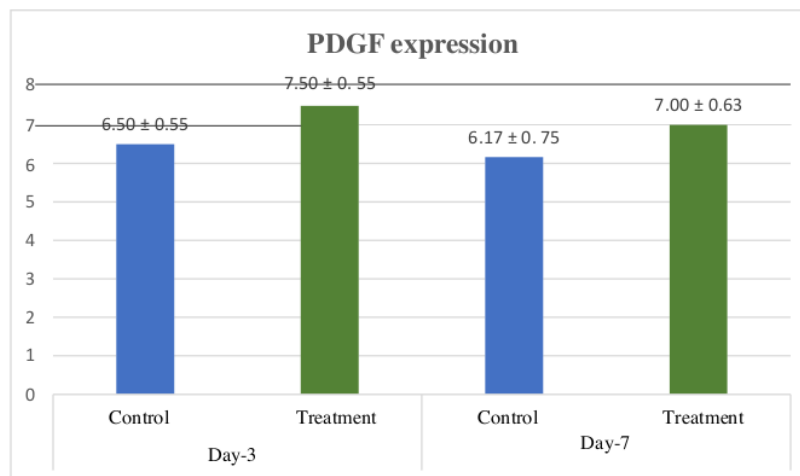


Image 1. Diagram of the mean PDGF expression around the incision wound of Wistar rats in the control and treatment groups on day 3 and day 7



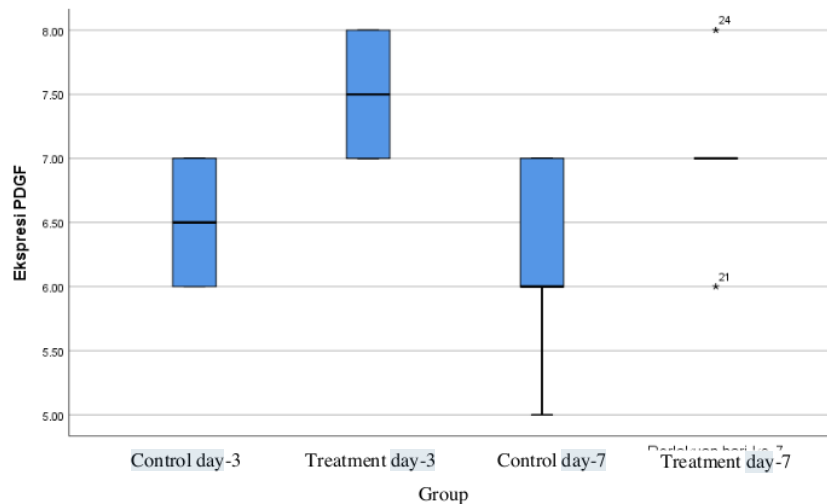


Image 2. Summary of the sample distribution of the PDGF expression

To determine the comparison of the mean value of the PDGF expression between groups of variables, namely the control group and the treatment group, the Kruskal-Wallis test was performed. If the results obtained are $p \text{ value} < \alpha = 0.05$, it can be interpreted that there is a significant difference. The results of the Kruskal-Wallis test showed a significant difference, namely the value of $p = 0.017$ ($p \text{ value} < 0.05$), which means that there was an effect of ropivacaine on changes in PDGF expression in rats' skin wound tissue.

Furthermore, the Mann Whitney Test was used to test whether there were significant differences between each group. From the results of the Mann Whitney test, the number of PDGF expressions on the 3rd day of the treatment group and the control group, it was found that the $p \text{ value} = 0.019$ ($p < 0.05$), this indicates that there was a significant difference between the treatment group (P1) and the control group (K1). While the number of PDGF expressions on day 7, between the treatment group (P2) and the control group (K2), it was



found that the value of $p = 0.067$ ($p > 0.05$), this indicates that the two groups were not significantly different.

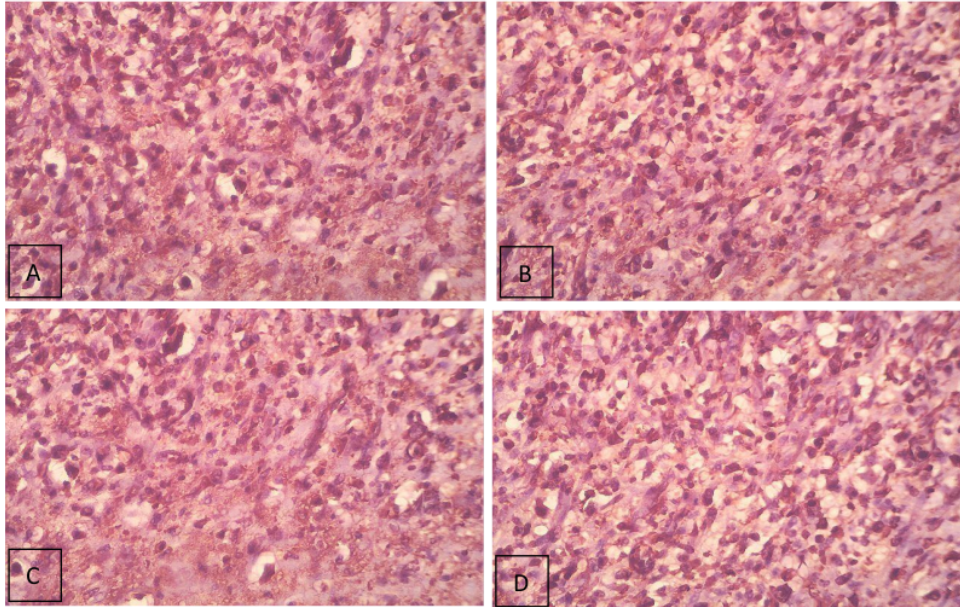


Image 3. PDGF expression on day 3 of skin incision wound tissue of Wistar rats using immunohistochemical staining with 400x magnification in the control group (A) and the treatment group (B). PDGF expression on day 7 in the control group (C) and the treatment group (D).

Neutrophil Cell Count

On anatomical histopathology examination, neutrophil cells appear polymorph nuclei consisting of three to five irregular oval or horseshoe-shaped lobes, which are connected to each other by fine chromatin threads and are purple in color, while the cytoplasm of neutrophils appears more transparent with fine purple or pink granules



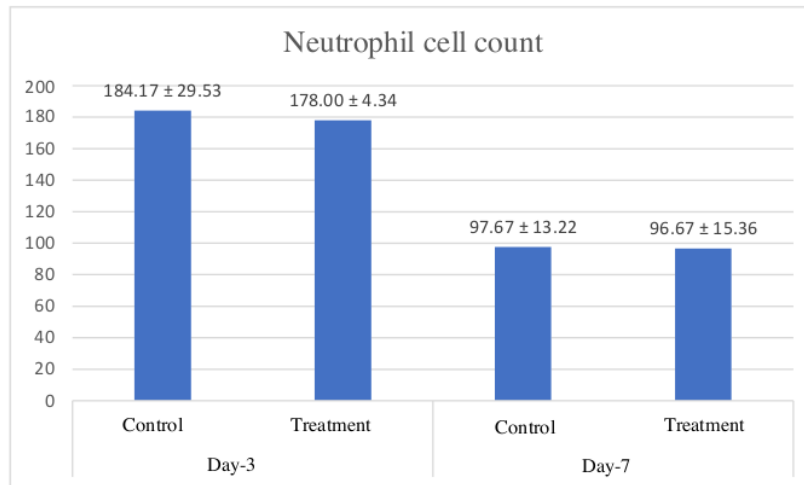


Image 4. Diagram of the mean number of neutrophil cells around the incision wound of Wistar rats in the control and treatment groups on day 3 and day 7

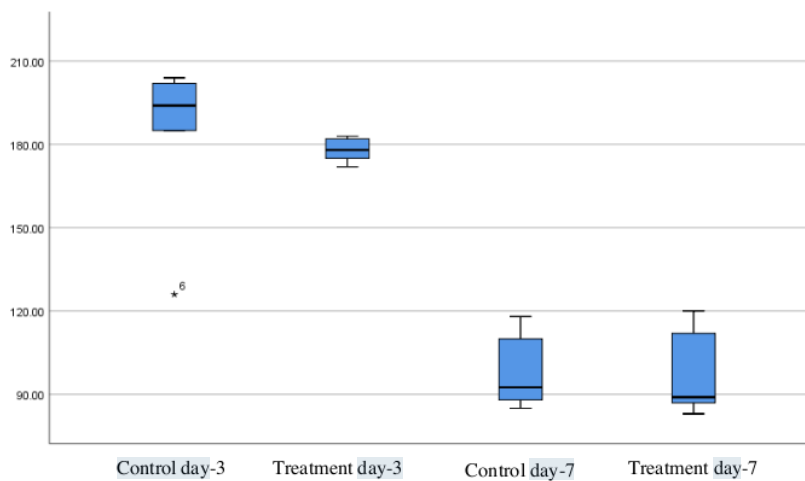


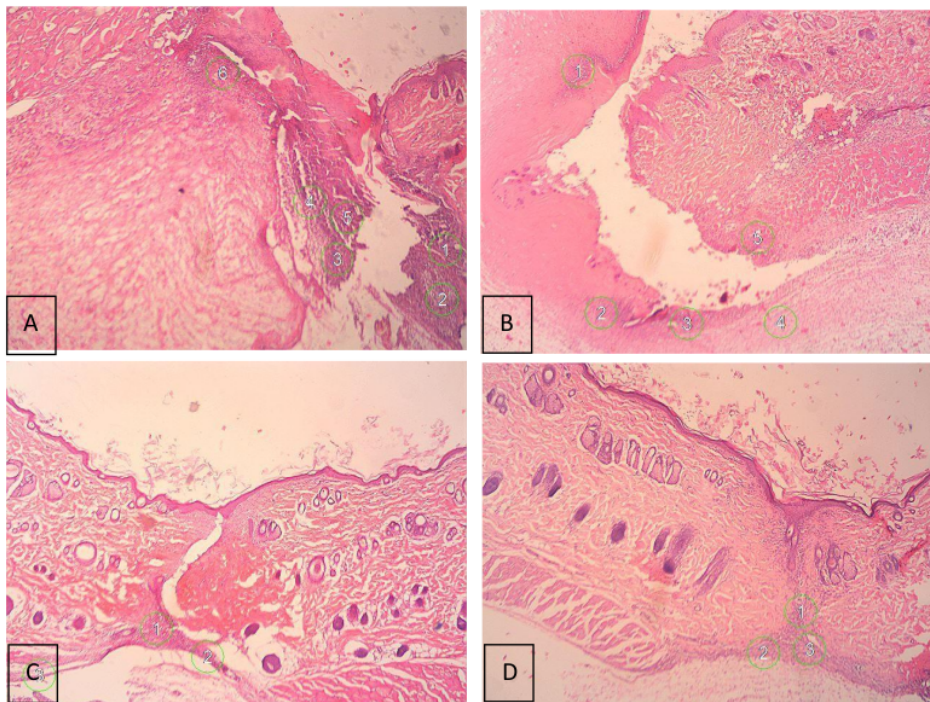
Image 5. Summary of sample distribution of neutrophil cells

On day 3, the results of counting the average number of neutrophil cells in the control group were 184.17 and in the treatment group were 178.00. Meanwhile, on the 7th day, the



15 results of counting the average number of neutrophil cells in the control group were 97.67 and 96.67 in the treatment group.

23 Then performed statistical analysis tests between control and treatment groups on the 3rd and 7th day. First, the normality test was carried out in each group using the Kolmogorov-Smirnov test. If the results obtained are $p \text{ value} > \alpha = 0.05$, it can be interpreted that the data distribution is normal. On day 3, the control group obtained $p = 0.025$, and the treatment group obtained $p = 0.200$. Meanwhile, on day 7, the control group obtained $p = 0.086$ and the treatment group obtained $p = 0.035$. So it can be concluded that all data in each group are not normally distributed.



14 **Image 6.** The number of neutrophil cells on day 3 in the skin incision wound tissue of Wistar rats using immunohistochemical staining with a microscope magnification of 100x in the control group (A) and the treatment group (B). The number of neutrophil cells on day 7 in the control group (C) and the treatment group (D).



To determine the comparison of the average number of neutrophil cells between variable groups, namely the control group and the treatment group, the Kruskal-Wallis test was performed. If the results obtained are $p \text{ value} < \alpha = 0.05$, it can be interpreted that there is a significant difference. The Kruskal-Wallis test results showed a significant difference, namely the value of $p = 0.000$.

Furthermore, the Mann Whitney Test was used to test whether there were significant differences between each group. From the results of the Mann Whitney test the number of neutrophil cells on day 3 of the treatment group and the control group, it was found that the $p \text{ value} = 0.055$ ($p > 0.05$), this indicates that between the treatment group (P1) and the control group (K1) there was no different meaning. While the number of neutrophil cells on the 7th day, between the treatment group (P2) and the control group (K2), it was found that the value of $p = 0.688$ ($p > 0.05$), this indicates that the two groups were not significantly different.

DISCUSSION

One of the important phases in the wound healing process after the wound is wound is the hemostatic process.¹⁰ Platelets play an important role in hemostasis, which is the first stage in tissue repair. Exposure to circulating platelets to the injured collagen tissue causes activation, aggregation and adhesion to the damaged endothelium. After activation of the coagulation process, fibrinogen is converted to fibrin. Fibrinogen in the wound area gives rise to a clotting mechanism resulting in coagulation (blood without cells and platelets) and together with the formation of fibrin tissue, it produces clotting in the wound which causes bleeding to stop. Activated blood platelets release proteins that induce the migration and



adhesion of neutrophils and monocytes, as well as several growth factors that promote wound healing.¹¹

One of the important growth factors in the hemostasis process is PDGF. PDGF plays a role in every phase of the wound healing process. PDGF is released from the degranulation of platelets in the wound and is present in wound fluid. PDGF stimulates mitogenicity and chemotaxis of neutrophils, macrophages, fibroblasts, and smooth muscle cells to the wound site by initiating an inflammatory response.¹² During the epithelization phase of the wound healing process, PDGF regulates or regulates the production of insulin growth factor 1 (IGF-1) and thrombospondin-1. PDGF also increases fibroblast proliferation and consequently ECM production, induces a myofibroblast phenotype and stimulates fibroblasts to create a collagen matrix. PDGF has decreased levels in chronic wounds because of its susceptibility to the proteolytic environment found in chronic wounds.¹³

In this study, it was found that the number of PDGF expressions was more in the treatment group than in the control group. Statistically, the observation on day 3 showed a significant difference, whereas on day 7 the amount of PDGF expression was also higher in the treatment group than in the control group, although it was not statistically significant. This finding is related to the physiological process in wound healing, where in the early phase (days 0–1) of the occurrence of the wound, PDGF levels reach high concentrations, and the levels then decrease acutely at the next stage of wound healing, until they reach a stable phase in the wound healing process 5-6th day.¹⁴

Pain is a stressor that triggers clinical pathophysiological symptoms, triggers modulation of the immune response, thereby causing a decrease in the immune system which results in prolonged wound healing. Pain that is not managed properly will prolong the



catabolic phase of increased glucagon, corticosteroids and insulin resistance.²¹ Increased glucocorticoid hormone becomes one of the systemic factors that hinders the wound healing process. The administration of ropivacaine infiltration around the wound can reduce the pain intensity so that it can reduce the secretion of glucocorticoid hormones so that it can accelerate the acute inflammatory process which is characterized by how many neutrophils. The faster the acute inflammatory process occurs, the faster the number of neutrophils is replaced by macrophages.²² Research conducted on animals and humans has shown that ropivacaine is less toxic than bupivacaine.⁴

The increase in the amount of PDGF expression in the treatment group compared to the control group was also due to the administration of ropivacaine which reduced the pain intensity in the incision wound. In a painful condition, the level of β endorphins secreted by the pituitary gland increases and suppresses macrophages so that the activity of macrophages which is influenced by IFN γ decreases. The decrease in macrophage activity will result in decreased cytokine activity released by macrophages such as TNF α , IL-1, IL-6, IL-8, PDGF, VEGF and TGF β to decrease.¹⁵ A decrease in some of these growth factors will result in inhibition of wound healing. In a state of pain, there is also an increase in the hormone cortisol and inhibits other growth factors, namely IL-1, which works to stimulate cells for the formation of procollagenase for the collagenase process.¹⁶

This is consistent with Cheng's study in 2007 which explained that topical application of rhPDGF significantly accelerated the rate of reepithelization compared to the untreated and treated group 7 days after being given the wound. These results suggest that application of rhPDGF increases cell proliferation, and improves dermal tissue repair in diabetic mouse skin lesions, which may be partly mediated by ERK activation and c-fos protein expression.¹⁷



Inflammation or inflammation that occurs after the injury is a response to the body's defense and this is normal. This inflammation is very important and needed by the body to carry out self-defense in order to eliminate debris and germs in the injured area. The inflammatory process can take place quickly and can also last a long time. As a marker of the duration of the acute inflammatory phase is the number of neutrophils.¹⁸ In the acute inflammatory phase, vascular permeability will increase, this will bring a lot of neutrophils to infiltrate the wound and carry out phagocytosis against debris and existing germs. However, if the neutrophils last for a long time in the wound area, it will interfere with the wound healing process. This is caused by neutrophil proteinase which can cause a decrease in body protein that should be used for the repair process, and also neutrophils will produce free radicals that inhibit wound healing.^{19,20} When entering the proliferation stage, neutrophils will fall and are replaced by macrophages.

In this study, the number of neutrophil cells was observed on day 3 and day 7 in the control and treatment groups. The results showed that there was a decrease in the number of neutrophil cells in the treatment group compared to the control group, both on the 3rd day and 7th day of the sample observation. And after 7th calculation was done statistically the results were not significantly different either on the 3rd day or the 7th day. This decrease in the number of neutrophil cells, which was not statistically significant, could be due to the physiological characteristics of the neutrophils in the wound healing process. At physiological mechanisms, post-injury neutrophil influx increases most rapidly during the first 12 hours and reaches a maximum value between days 1 and 2, and levels are stable (plateau) to day 3, and drop dramatically on day 5.²³ The results of this study indicate that administration of ropivacaine can reduce the number of neutrophil cells through the inhibition



of pain impulses which in turn will accelerate the completion of the inflammatory phase. This may also be due to the antibacterial effect of ropivacaine as an in vitro study by Jadhav et al.²⁴ From the observations, it can also be seen that there was a significant decrease in the number of neutrophil cells on the 7th day when compared to the 3rd day in both the control group and the treatment group. This is in accordance with the theory that the number of neutrophil cells will decrease during the proliferation process and their role is replaced by macrophages.²⁵

Some of the limitations in this study include the possibility of genetic variability of experimental animals, and animal behavior related to environmental conditions, which can affect variations in response to experimental treatment.²⁶ although various attempts have been made to homogenize the object of research.

CONCLUSION

In the end it can be concluded that giving ropivacaine infiltration around the incision wound can increase the expression of Platelet Derived Growth Factor (PDGF), and reduce the number of neutrophil cells in the wound healing process on the 3rd and 7th day of observation. It is necessary to do a similar study by taking a longer period to determine the dynamics of PDGF and neutrophil expression at each phase of wound healing. Examination of the expression of more specific cells or proteins can be a means of deepening understanding of the mechanisms in this intervention.

REFERENCES

1. Strichartz GR. Novel ideas of local anaesthetic actions on various ion channels to ameliorate postoperative pain. *Br J Anaesth.* 2008;101(1):45–7.
2. Cassuto J, Sinclair R, Bonderovic M. Anti-inflammatory properties of local anaesthetic



- and their present and potential clinical implications. *Acta Anaesthesiol Scand.* 2006;50(6):265–82.
3. Whiteman A, Bajaj S, Hasan M. *Novel Techniques of Local Anaesthetic Infiltration.* Oxford Univ Press behalf Br J Anaesth. 2011;Continuing.
 4. Pramono W, Leksana E, Satoto H. Pengaruh Pemberian Ropivakain Infiltrasi Terhadap Tampilan Kolagen di Sekitar Luka Insisi Pada Tikus Wistar. *J Anesthesiol Indones.* 2016;VIII(7):1–10.
 5. Paul W, Sharma C. *Advances in Wound Healing Materials: Science and Skin Engineering.* Smithers Shropsh. 2015;4(36).
 6. Gan T. Poorly controlled postoperative pain : prevalence, consequences, and prevention. *J Pain Res.* 2017;10(2):287–98.
 7. Suwiknyo P, Sumartono C, Susila D, Sulistiawan S. Hubungan Tingkat Kepatuhan Petugas Medis dalam Menjalankan Panduan Tata laksana Nyeri dengan Kepuasan Pasien Pascaoperasi dan Skor Nyeri saat Keluar Rumah Sakit di RSUD dr. Soetomo Surabaya. Univ Airlangga; 2017.
 8. Suhardjono D. *Percobaan Hewan Laboratorium.* Yogyakarta: Gajah Mada University Press; 1995. 207 p.
 9. Barrientos S, Stojadinovic O, Golinko M., Brem H, Tomiccanic M. Growth factors and cytokines in wound healing. *Wound Healing Society. Wound Rep Reg.* 2008;16:585–601.
 10. Guo S, Dipietro LA. Factors Affecting Wound Healing. *J Dent Res.* 2010;89(3):219–29.
 11. Eisinger F, Patzelt J, Langer HF. The Platelet Response to Tissue Injury. *Front Med.* 2018;5(November):1–15.
 12. Abrao J, Antunes M, Garcia L. Local Anaesthetic Infiltration and Wound Healing Process. *IntechOpen.* 2019;
 13. Badiu D, Vasile M, Teren O. Regulation of Wound Healing by Growth Factors and Cytokines. In: Middleton J., editor. *Wound Healing: Process, Phases, and Promoting.* New York: Nova Science Publishers, Inc; 2011. p. 76–8.
 14. Aiba-kojima E, Tsuno NH, Inoue K, Matsumoto D. Characterization of wound drainage fluids as a source of soluble factors associated with wound healing : Comparison with platelet-rich plasma and potential use in cell culture Characterization of wound drainage fluids as a source of soluble factors associ. *Wound Repair Regen.* 2007;15(October):511–20.
 15. Shrihari T. Beta-Endorphins: A Novel Anti-Inflammatory Activity. *EC Pharmacol Toxicol.* 2019;7(6):481–4.
 16. Omoigui S. The Biochemical Origin of Pain – Proposing a new law of Pain: The origin of all Pain is Inflammation and the Inflammatory Response PART 1 of 3 – A unifying law of pain. *Med Hypotheses.* 2007;69(1):70–82.
 17. Cheng B, Liu H-W, Fu X-B, Sun T-Z, Sheng Z-Y. Recombinant human platelet-



- derived growth factor enhanced dermal wound healing by a pathway involving ERK and c-fos in diabetic rats. *J Dermatol Sci.* 2007;45(3):193–201.
18. Hall ACGJE. *Textbook of Medical Physiology*. 11th ed. Philadelphia: Elsevier; 2006.
 19. Ellis S, Lin E., Tartar D. Immunology of Wound Healing. *Curr Dermatol Rep.* 2018;7:350–8.
 20. Landen N, Li D, Stahle M. Transition from Inflammation to Proliferation: a critical step during Wound Healing. *Cell Mollecular Life Sci.* 2016;73(20):3861–85.
 21. Şimşek T, Şimşek HU, Cantürk NZ. Response to trauma and metabolic changes : posttraumatic metabolism. *Ulus Cer Derg.* 2014;30:153–9.
 22. Mikawa K, Akamatsu H, Nishina K, Shiga M, Obara H, Niwa Y. Effects of ropivacaine on human neutrophil function : comparison with bupivacaine and lidocaine. *Eur J Anaesthesiol.* 2003;20: 104–10.
 23. Kim M, Liu W, Borjesson DL, Curry FE, Miller LS, Cheung AL, et al. Dynamics of Neutrophil Infiltration during Cutaneous Wound Healing and Infection Using Fluorescence Imaging. *J Invest Dermatol.* 2008;128(7):1812–20.
 24. Jadhav V, Jadhav R, Diwanmal B. Ropivacaine A Review of Its Use In Regional Anaesthesia, Choric Pain Management And In Patients With Cardiac Diseases In Non Cardiac Surgeries. *IOSR J Pharm Biol Sci.* 2015;10(1 Ver. 1):43–7.
 25. Kumar KP, Nicholls AJ, Wong CHY. Partners in crime : neutrophils and monocytes / macrophages in inflammation and disease. *Cell Tissue Res.* 2018;371:551–65.
 26. National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals. *Guide for the Care and Use of Laboratory Animals*, 8th edition. Washington DC: National Academy of Sciences; 2011.



Scopus Support (ELS) <ScopusSupport@elsevier.com>

Nov 22,
2020, 5:39
PM

to me

Dear Imam Susilo,

Thank you for your enquiry.

Ticket number 201122-011427 has been opened on your behalf and we aim to respond within 48 hours(excluding weekends). Please be advised that it may take up to four weeks for any relevant corrections to be completed. We appreciate your patience in this matter.

For missing requests, we will attempt to source one on your behalf, but this may result in delay in resolving your request or your request being returned if a PDF cannot be sourced.

Please use this ticket number in any future correspondence and please do not change the subject line of this email when you reply.

For further support information please visit our [Scopus: Profile and content corrections Support Center](#).

Regards,

ELSEVIER | Scopus- Content Service Desk

From: Imam Susilo

Date: 22/11/2020 10.39 AM

I have published an article in the SYLWAN Vol 164 Issue 09 entitled "Effect of Ropivacaine Around the Incision on the Expression of Platelet Protein Derived Growth Factor and Neutrophil Cell Infiltration in the Wound Healing Process (Experimental Laboratory Study on Wistar Rats)", but the article has not been indexed in the www.scopus.com

This email is for use by the intended recipient and contains information that may be confidential. If you are not the intended recipient, please notify the sender by return email and delete this email from your inbox. Any unauthorized use or distribution of this email, in whole or in part, is strictly prohibited and may be unlawful. Any price quotes contained in this email are merely indicative and will not result in any legally binding or enforceable obligation. Unless explicitly designated as an intended e-contract, this email does not constitute a contract offer, a contract amendment, or an acceptance of a contract offer.

Elsevier Limited. Registered Office: The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, United Kingdom, Registration No. 1982084, Registered in England and Wales. [Privacy Policy](#)



ReplyForward



Effect of Ropivacaine Around the Incision on the Expression of Platelet Protein Derived Growth Factor and Neutrophil Cell Infiltration in the Wound Healing Process (Experimental Laboratory Study on Wi

ORIGINALITY REPORT

19%

SIMILARITY INDEX

14%

INTERNET SOURCES

11%

PUBLICATIONS

7%

STUDENT PAPERS

PRIMARY SOURCES

- 1 Tamer Kamal, Sunil Garg, Kareem Elsorafy, Anca Duca. "Surgical Management of Fracture Neck of Femur in a Medically Unfit ASA3/4 Patient Selection Using Direct Infiltration Local Anaesthesia", Open Journal of Orthopedics, 2014
Publication 1%
- 2 Submitted to All India Institute of Medical Sciences, Rishikesh
Student Paper 1%
- 3 journal2.unusa.ac.id
Internet Source 1%
- 4 erepository.uonbi.ac.ke
Internet Source 1%
- 5 Submitted to Ain Shams University
Student Paper 1%

6	Joshua S. Boateng. "Wound healing dressings and drug delivery systems: A review", Journal of Pharmaceutical Sciences, 08/2008 Publication	1 %
7	f1000research.com Internet Source	1 %
8	Submitted to University of Sheffield Student Paper	1 %
9	www.dovepress.com Internet Source	<1 %
10	Emiko Aiba-Kojima. "Characterization of wound drainage fluids as a source of soluble factors associated with wound healing: comparison with platelet-rich plasma and potential use in cell culture", Wound Repair and Regeneration, 7/2007 Publication	<1 %
11	docksci.com Internet Source	<1 %
12	www.frontiersin.org Internet Source	<1 %
13	www.wjgnet.com Internet Source	<1 %
14	cyberleninka.org Internet Source	<1 %

15	erepo.unud.ac.id Internet Source	<1 %
16	heanoti.com Internet Source	<1 %
17	static.sliit.lk Internet Source	<1 %
18	thieme-connect.com Internet Source	<1 %
19	www.mdpi.com Internet Source	<1 %
20	"Stem Cells in Aesthetic Procedures", Springer Nature, 2014 Publication	<1 %
21	Submitted to University of Ulster Student Paper	<1 %
22	link.springer.com Internet Source	<1 %
23	www.researchsquare.com Internet Source	<1 %
24	MARIA A. BARNADAS. "EFFECT OF TOPICAL TRETINOIN ON EPIDERMAL LANGERHANS' CELLS IN PHOTODAMAGED SKIN", International Journal of Dermatology, 8/1995 Publication	<1 %

25	Submitted to University of New England Student Paper	<1 %
26	docshare.tips Internet Source	<1 %
27	vital.seals.ac.za:8080 Internet Source	<1 %
28	Submitted to Kenyatta University Student Paper	<1 %
29	Submitted to Manchester Metropolitan University Student Paper	<1 %
30	akademik.unsoed.ac.id Internet Source	<1 %
31	eprints.undip.ac.id Internet Source	<1 %
32	journal.stikep-ppnijabar.ac.id Internet Source	<1 %
33	www.thieme-connect.com Internet Source	<1 %
34	inba.info Internet Source	<1 %
35	protocolexchange.researchsquare.com Internet Source	<1 %

36

Eighty Mardiyani Kurniawati, Citra Aulia Bachtiar, Hermanto Tri Joewono, Budi Utomo. "Knowledge and confidence levels improvement among obstetrics residents regarding caesarean section training using video-mannequins combination", Heliyon, 2023

Publication

<1 %

37

Nafise Amiri, Andrew P. Golin, Reza B Jalili, Aziz Ghahary. "Roles of Cutaneous Cell - Cell Communication in Wound Healing Outcome: Emphasis on Keratinocyte - Fibroblast Crosstalk", Experimental Dermatology, 2021

Publication

<1 %

38

Anna A. Borovikova, Mary E. Ziegler, Derek A. Banyard, Garrett A. Wirth et al. "Adipose-Derived Tissue in the Treatment of Dermal Fibrosis", Annals of Plastic Surgery, 2018

Publication

<1 %

39

Submitted to Grenoble Ecole Management

Student Paper

<1 %

40

Meng Sun, Helin Zhang, Min Jiang, Yan Chai, Jianxun Qi, George F. Gao, Shuguang Tan. "Structural insights into the cis and trans assembly of human trophoblast cell surface antigen 2", iScience, 2021

Publication

<1 %

41	Siqi Wang, Nai Zhang, Bowen Jiang, Bo Lönnerdal, Yue Chen, Bing Wang. "Molecular Characterization and Expression of Lactoferrin Receptor (LfR) in Different Regions of the Brain Responding to Lactoferrin Intervention: a Mechanism for Neurodevelopment and Cognition in Piglets", Research Square Platform LLC, 2023 Publication	<1 %
42	d.lib.msu.edu Internet Source	<1 %
43	eprints.usm.my Internet Source	<1 %
44	minerva-access.unimelb.edu.au Internet Source	<1 %
45	rc.library.uta.edu Internet Source	<1 %
46	repositorium.sdum.uminho.pt Internet Source	<1 %
47	www.hal.inserm.fr Internet Source	<1 %
48	www.karger.com Internet Source	<1 %
49	www.medscidiscovery.com Internet Source	<1 %

50

Floris Dammeijer, Lysanne A. Lievense, Margaretha E. Kaijen-Lambers, Menno van Nimwegen et al. "Depletion of Tumor-Associated Macrophages with a CSF-1R Kinase Inhibitor Enhances Antitumor Immunity and Survival Induced by DC Immunotherapy", Cancer Immunology Research, 2017

Publication

<1 %

51

Yuzi Xu, Chuan Zhou, Jia Li, Yangbo Xu, Fuming He. " - based proteomic analysis reveals potential osteogenesis - promoted role of in strontium - incorporated titanium implant ", Journal of Biomedical Materials Research Part A, 2021

Publication

<1 %

52

Stephan Barrientos. "Growth factors and cytokines in wound healing", Wound Repair and Regeneration, 09/2008

Publication

<1 %

Exclude quotes Off

Exclude matches Off

Exclude bibliography On

Effect of Ropivacaine Around the Incision on the Expression of Platelet Protein Derived Growth Factor and Neutrophil Cell Infiltration in the Wound Healing Process (Experimental Laboratory Study on Wi

GRADEMARK REPORT

FINAL GRADE

/100

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12

PAGE 13

PAGE 14

PAGE 15

PAGE 16

PAGE 17

PAGE 18

