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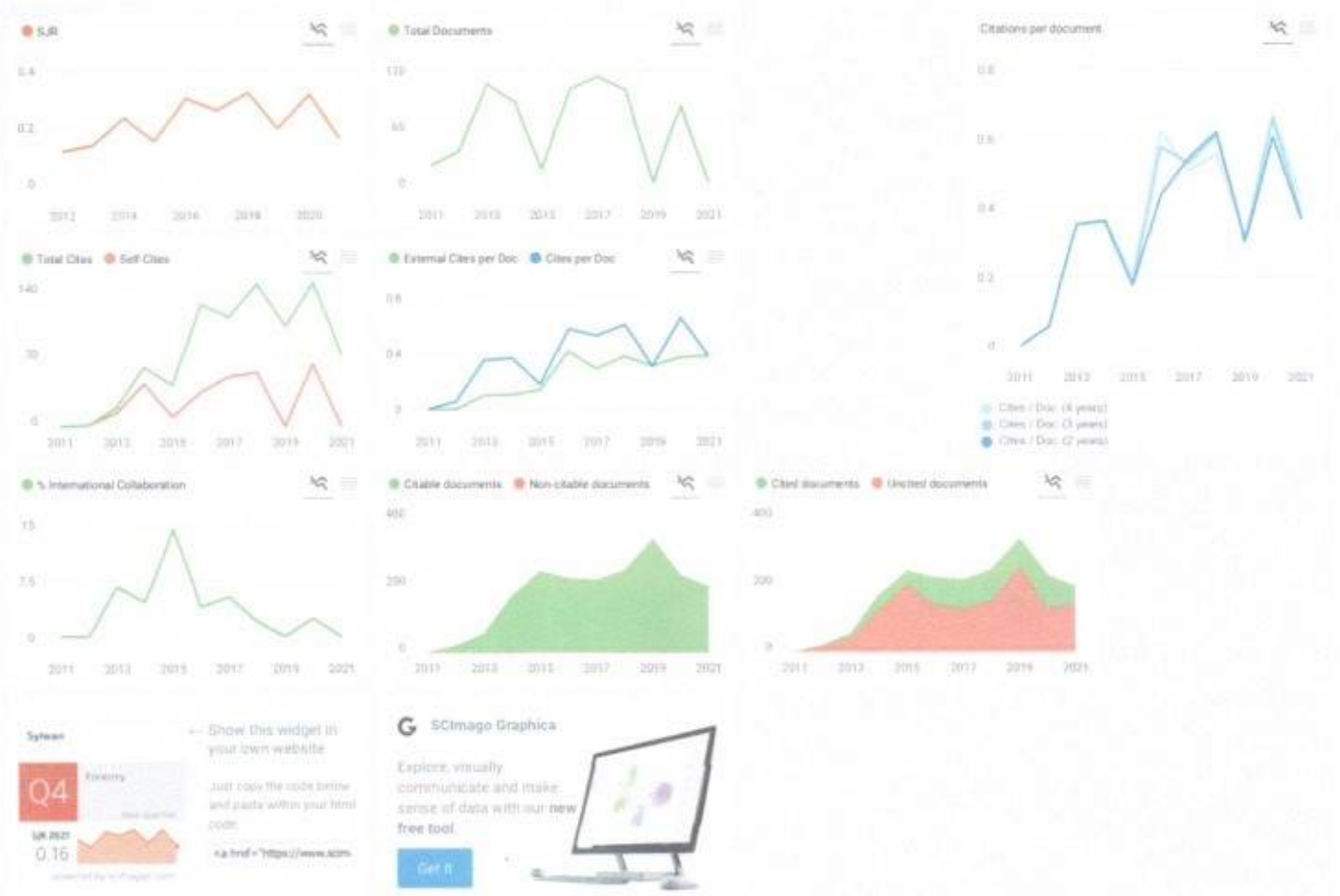

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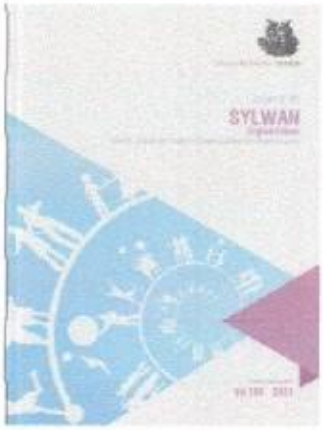

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Effect of Ropivacaine Infiltration in Incisional Wound on Fibroblast Growth Factor (FGF) Expression and Collagen Thickness in Wound Healing

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ABSTRACT

Background: Wound healing process includes cellular and biochemistry response that consists of a few phases involving various factors. Fibroblast growth factor (FGF) and collagen plays important roles in wound healing. One of the methods that accelerates wound healing process is by eliminating pain, which can be achieved by infiltration of local anaesthesia (LA). This study aims to determine the effect of ropivacaine infiltration as local anaesthesia in the expression of FGF and collagen.
Methods: This study is an experimental study with randomized post-test only control group design. The samples of this study were 24 Wistar rats selected in Experimental Animal Unit of Pharmacology Department of Airlangga Medical Faculty that fulfilled inclusion and exclusion criteria. The rats underwent acclimatization period, divided into four groups then incised, either followed by 1 ml ropivacaine 0.2% infiltration or left as is. Excisional biopsy procedures were done on third and seventh day to examine the expression of FGF and collagen thickness. Data was then analysed by SPSS.
Results: Compared to control group, the incisional wounds of rats that underwent ropivacaine 0.2% infiltration on the third day showed significant difference of FGF expression ($U=2.5$; p-value=0.006) and collagen thickness ($t(10)=52.8$; p-value<0.001) but not on the seventh day.
Conclusion: In conclusion, ropivacaine 0.2% infiltration showed significant difference in the expression of FGF and collagen thickness on the third day after incision, therefore further studies regarding the effects of ropivacaine infiltration to enhance wound healing still needed to be done.

Keywords*: Collagen, FGF, Local anaesthesia, Ropivacaine, Wound healing*

INTRODUCTION

Wound healing process includes cellular and biochemistry response that starts from haemostatic phase, inflammation phase, proliferation phase, and ends with maturation phase. A cell that plays a crucial role in this process is macrophage, the one that is in charge of the secretion of growth factors and cytokines, both pro-inflammatory and anti-inflammatory. One

of the growth factors produced by macrophage is fibroblast growth factor (FGF) that affects granulation formation, re-epithelisation and remodelling of tissue. In-vitro studies show that FGF increases keratinocyte motility during re-epithelisation, induces fibroblast migration and stimulates fibroblast to produce collagen. Extracellular matrix is replaced by type-3 collagen in acute phase, which will then be replaced by type-1 collagen in maturation phase. [1,2]

One of the methods that accelerates wound healing process is by eliminating pain, which can be achieved by infiltration of local anaesthesia (LA). Ropivacaine is one of long-acting amide LA and produced as pure enantiomers. Benefits of infiltration of ropivacaine in excision wound is not limited to its anti-nociceptive characteristic but also its bacteriostatic and bactericidal properties. LA has been known to affect higher histologic inflammation marker in day 3 after incision,[3,4] but other studies also have shown negative effect on wound healing.[5] Nevertheless, infiltration of LA in operative procedures have shown positive impact in speeding up mobilisation and better pain management therefore decreasing the analgesics needed.[6,7] By this study we aim to determine the effect of ropivacaine infiltration as local anaesthesia in the expression of FGF and collagen that have important roles in wound healing.

MATERIAL AND METHOD

Study Sample

This study is an experimental study with randomized post-test only control group design. The samples of this study were Wistar rats that fulfilled inclusion criteria: pure breeds of Wistar rats, aged two to two and a-half months, weighed 250 to 300 grams and did not have any anatomical anomalies. The exclusion criteria of the samples were those who were

sick during the 7-days acclimatization period and those who were sick and died after intervention. The rats concluded in this study was selected in Experimental Animal Unit of Pharmacology Department of Airlangga Medical Faculty. Wistar rats' selection were conducted considering the inclusion and exclusion criterias of the study.

The sample size was calculated using Federer formula and the result obtained was 24 rats. The samples were then divided randomly into four groups, group I1; the rats that were incised 2cm and given ropivacaine 0,2% infiltration and evaluated on day 3 after incision; group I2; the rats that were incised 2cm and given ropivacaine 0,2% infiltration and evaluated on day 7 after incision; group C1; the rats that were incised 2cm and evaluated on day 3 after incision; and group C2 the rats that were incised 2cm and evaluated on day 7 after incision.

Research Procedure

Wistar rats underwent acclimatization for seven days prior to experiment to adapt with study environment. Samples were given same food and drink and weighed every day during this period. After acclimatization period, samples were divided randomly into four groups: I1, I2, C1 and C2, consisting of 6 rats in each group. The rats were then kept in 30x20x7cm cage according to their groups. All samples were anesthetized with ketamine-xylazine with the dose of 75-100mg/kgbw + 5-10mg/kgbw intraperitoneally for 10 to 30 minutes, the rats' backs were then shaved and disinfected with povidone iodine, before given a 2cm subcutaneous-deep incision wound. Incision wounds were then disinfected with povidone iodine and either given 1 ml ropivacaine 0,2% infiltration subcutaneously in I1 and I2 groups 0,5cm around them; or left as is in C1 and C2 groups and disinfected once again before wound dressing were applied.

On the third day after incision, the rats in I1 and C1 groups were anaesthetized with ketamine to undergo excisional biopsy procedures by taking $3cm^2$ tissue subcutaneous-deep. The same procedures were done to the rats in I2 and C2 groups on the seventh day after incision. The tissues obtained were then processed as histological specimen in paraffin blocks; undergoing fixation with formaline, dehydration process with alcohol, alcohol clearing process using xylol, impregnation in paraffin and paraffin block making. After paraffin blocks were made, the next procedure is hematoxylin and eosin staining. The tissues on the slides underwent deparaffinization in xylol and absolute ethanol, then hydration process using alcohol and water, stained with hematoxylin and eosin, dehydration using alcohol then alcohol clearing using xylol, and mounted using entelan and covered with deck glass. The slides were then examined by pathologists under microscopes for the expression of FGF and collagen thickness. The data was then obtained and analysed.

The data was then tested for its distribution normality using Kolmogorov-Smirnov, and analysed for its differences using parametric independent t-test for both normally distributed data and non-parametric Mann-Whitney U test for those that were not normally distributed. Data analysis was done using SPSS 17.0. P-value of <0.05 was considered statistically significant.

RESULTS

Fibroblast Growth Factor

Fibroblast growth factor (FGF) expression was examined using immunohistochemistry method using the excisional biopsy specimens from every rat in each group. Groups that

underwent ropivacaine 0.2% infiltration showed the highest FGF expression score, 7,17±0,41 and 7,24±0,52 respectively.

Table 1. FGF Expression Between Groups

Group	Min.	Max.	Mean	Std. deviation
C1	6	7	6,17	0,41
I1	7	8	7,17	0,41
C2	6	8	7,00	0,63
I2	7	8	7,67	0,52

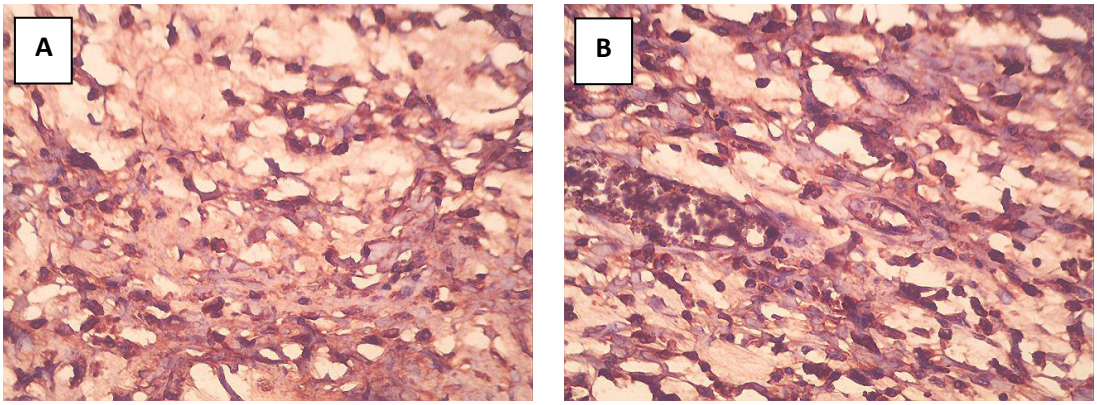

Fig.1 Expression of FGF on the third day after incision in wistar rats of group C1(A) and I1(B)

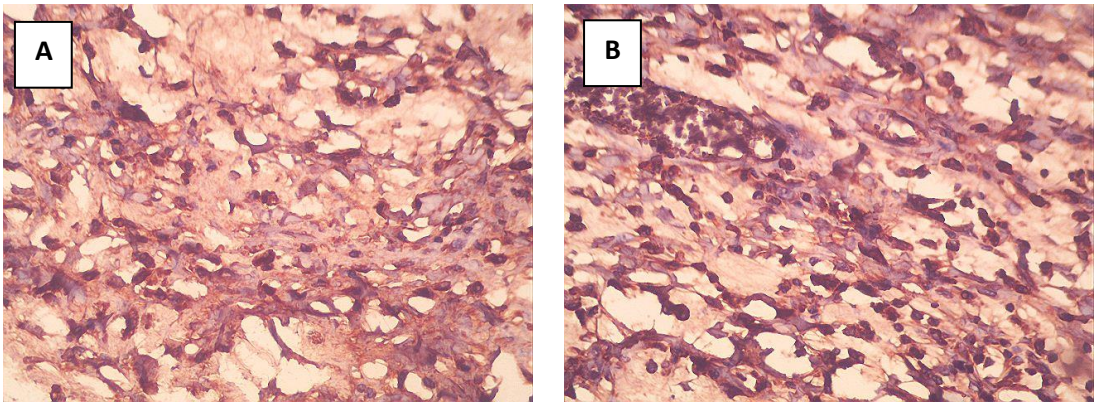

Fig.2 Expression of FGF on the seventh day after incision in wistar rats of group C2(A) and I2(B)

Collagen

Collagen expression was calculated using micrometer unit from excisional biopsy specimens.

Group I1 showed the thickest collagen compared to the other groups.

Table 2. Collagen thickness between groups

Group	Min.	Max.	Mean	Std. deviation
C1	8,8	10,2	9,55	0,49
I1	23,8	25,2	24,65	0,50
C2	14,3	18,2	17,10	1,41
I2	17,2	19,2	18,03	0,75

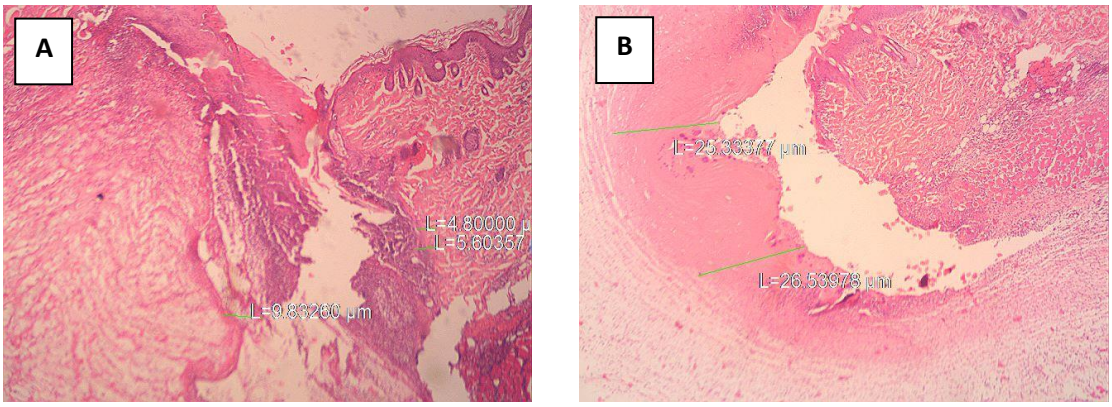

Fig. 3 Collagen on the third day after incision in wistar rats of group C1(A) and I1(B)

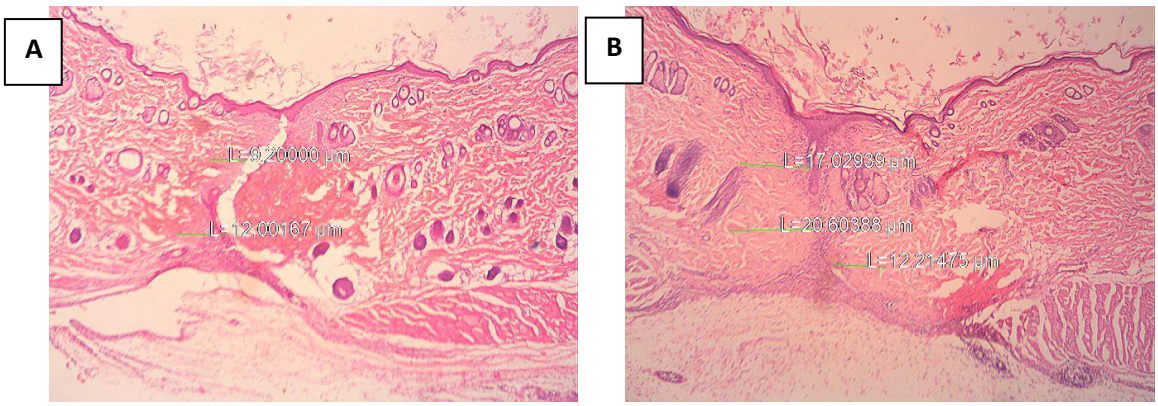

Fig. 4 Collagen on the third day after incision in wistar rats of group C1(A) and I1(B)

Comparison between ropivacaine (I1) and non-ropivacaine (C1) group on the 3rd day

On the third day, expression of FGF (U=2.5; p-value=0.006) and thickness of collagen (t(10)=52.8; p-value<0.001) showed significant difference between those that were infiltrated with ropivacaine 0.2% and those that were not.

Table 3. Analysis of FGF and collagen between group I1 and C1

Variable	Mann-Whitney U	p-value
FGF expression	2,5	0,006
Variable	**t(df)**	**p-value**
Collagen thickness	52,8(10)	<0,001

Comparison between ropivacaine (I2) and non-ropivacaine (C2) group on the 7th day

On the seventh day, expression of FGF (U=8.0; p-value 0.075) and collagen thickness (U=10.5; p-value 0.225) did not show any significant difference between those that underwent ropivacaine infiltration and those that did not.

Table 4. Analysis of FGF and collagen between group I2 and C2

Variable	Mann-Whitney U	p-value
FGF expression	8,0	0,075
Collagen thickness	10,5	0,225

Comparison between non-ropivacaine groups on the 3rd and 7th day

Expression of FGF did not show significant difference in between non-ropivacaine groups on the 3rd and 7th day (U=9.0; p-value=0.093) but showed a significant difference in collagen thickness (t(10)=17.9; p-value<0.001).

Table 6. Analysis of FGF and collagen between group C1 and C2

Variable	Mann-Whitney U	p-value
FGF expression	9,0	0,093

Variable	t(df)	p-value
Collagen thickness	17,9(10)	<0,001

Comparison between ropivacaine groups on the 3rd and 7th day

There was a significant difference in the expression of FGF (U=5.5; p-value=0.026) and collagen thickness (U=0.0; p-value=0.004) compared on the 3rd day and 7th day.

Table 5. Analysis of FGF and collagen between group I1 and I2

Variable	Mann-Whitney U	p-value
FGF expression	5,5	0,026
Collagen thickness	0,0	0,004

DISCUSSION

Fibroblast Growth Factor after ropivacaine infiltration and its role in wound healing

Compared to control group, the incisional wounds of rats that underwent ropivacaine 0.2% infiltration showed significant difference of FGF expression on the third day, but not on the seventh day. The expression of FGF on the 3rd and 7th day was significantly different in the control group, but not in the intervention group. This result showed that ropivacaine 0.2% infiltration increased the expression of FGF on the 3rd day after incision, and even without ropivacain 0.2% infiltration, expression of FGF still increased on the 7th day compared to the 3rd day. There has not been any prior study that aims to find the effect of ropivacaine infiltration on FGF expression.

FGF is an angiogenic factor that plays an important role in wound healing[1]. The result of angiogenesis is the formation of new blood vessels that supply blood and other factors that enhance wound healing.[9] One of the FGFs that has a huge impact on wound healing is FGF-

2, which increases on acute wounds and plays a role in formation of granulation tissue, reepithelisation, and tissue remodelling. FGF-2 controls synthesis and deposition of various components of extracellular matrix therefore increases keratinocyte motility during reepithelisation and induces fibroblast migration to produce collagenase. FGF-7 increases the transcription of factors that are in charge of ROS detoxification and is a strong mitogen for vascular endothels.[1, 10, 11] The use of FGF to enhance wound healing has been in various countries, such as China, in which the study showed that FGF-2 accelerated wound healing in burn[12] and enhanced the quality of scars on surgical wounds.[13, 14]

Collagen thickness after ropivacaine infiltration and its role in wound healing

The thickest collagen was found in ropivacaine group examined on the 3rd day. Similar to the result in FGF expression, collagen thickness between ropivacaine and non-ropivacaine groups showed significant difference on the 3rd day ($t(10)=52.8$; $p<0.001$), but not on the 7th day ($U=10.5$; $p=0.225$). Unlike FGF, there was a significant difference in collagen thickness compared on the 3rd and 7th day both in ropivacaine and non-ropivacaine groups. The result of this study is similar to the one conducted in Semarang, that showed a significant increase of collagen thickness in incision wounds infiltrated with levobupivacaine.[15]

Collagen is one of the basic structures that forms a tissue. It can be found on skin, mostly as collagen type I and type III. Collagen interacts with platelets and fibronectin, increase exudation, growth factors, cellular components and induces fibroplasia process. During trauma, it binds with fibronectin therefore activates platelets and induces platelets aggregation, and releases chemotactic factors that start the process of wound healing. Triple

helix structure of collagen is essential fol platelet aggregation. Type III collagen has been reported more effective in platelet aggregation rather than type I and type II. Collagen fragments release leucocytic collagenases to attract fibroblasts to tissue in trauma. Collagen will then be the base of new extracellular matrix. The increase of collagen is simultaneous with wound healing acceleration. Even so, in trauma, normal collagen is replaced by scar collagen which tensile strength only reaches 80% of normal collagen.[2, 16]

LA infiltration in wound healing

There have been various studies in the role of local anaesthesia in wound healing that also showed a variety of results. One of the first studies about this was conducted in 1984 by makin a midline incision on rabbits' abdomen. The result of this study showed no significant difference on the group that was given LA infiltration[17], but another study in Brazil showed that on the 3rd day, the number of macrophages, TGF β-1 and collagen fibres are increased in the rats that underwent LA infiltration, but the quality of wound healing after 14 days did not show any significant difference.[3] As opposed to this study, a research in Turkey showed that LA infiltrated wounds had lower tensile strength compared to control group, that means it had negative effect on wound healing on th 21st day.[5]

LA might have positive effect on wound healing by reducing stress response and pain, that also play an important role in inflammation and proliferation phase.[4,18] Another effect of LA that might be beneficial in wound healing is its bacteriostatic and bactericidal properties.[19] On the other hand, LA also has negative effects on wound healing because of its anti-proliferative effect on mesenchymal cells.[20] Studies about effects of LA on microcirculation also showed variation of results. Cocaine, even in low dose, induces

vasoconstriction by inhibiting norepinephrine uptake; but newer generation LA such as lidocaine and bupivacaine had a dose-dependent effect, with low dose it induces arteriole vasoconstriction, but in higher dose it induces vasodilation, but can also differ in geriatric patients because of lower blood flow and hepatic clearance.[21, 22]

CONCLUSION

Ropivacaine 0.2% infiltration increased the expression of FGF and collagen thickness on the third day after incision, therefore further studies regarding the effects of ropivacaine infiltration to enhance wound healing still needed to be done.

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