大韓外官科學會誌 : 第12卷 第1號
The Journal of Oriental Medical Surgery, Ophthalmology & Otolaryngology
Vol. 12, No 1, February 1999.

The Effects of Jawoongo plus *Rehmanniae Radix* on The Wound Healing of Rats

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ABSTRACT

Herbal medicines are popular in Korea communities and used for a variety of diseases, and most herbal medicines has been used an oral administration for treating diseases, but some herbal medicines included Jawoongo has been used by applying on the skin. Jawoongo, a traditional oriental medicine ointment, have been used for treating various dermatitis associated with skin diseases such as tinea manuum, eczema and chilblain, etc. by promoting blood flow(活血), dispersing wind(散風) and moistening(潤燥).

Jawoongo used in this study is derived from Yungigo supplemented with *Adeps Suillus* (豚脂).

The aim of this study is to investigate the effect of Jawoongo plus *Rehmanniae Radix*(生地黃) on the healing of incisional skin wound in rats. After inducing an inflammation on the rats, we observed the amount of Leukocyte, the level of Cortisol and CRP(C-reactive protein), the histological parts and have obtained the healing effect of wound by using Jawoongo plus *Rehmanniae Radix*(生地黃).

※ 이 논문은 1998학년도 동의대학교 자체 학술연구조성비의 지원을 받아 작성되었음.

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Ⅰ. Introduction

Herbal medicines are popular in Korea communities and used for a variety of diseases, and most herbal medicines has been used an oral administration for treating diseases, but some herbal medicines included Jawoongo has been used by applying on the skin. Jawoongo, a traditional oriental medicine ointment, have been used for treating various dermatitis associated with skin diseases such as tinea manuum, eczema and chilblain, etc(1-4).

Jawoongo used in this study is derived from Yungigo supplemented with *Adeps Suillus* (豚脂). Yungigo was originally prescribed by Jin(5) for scabby scalp and has been widely applied in cutaneous diseases(1, 6).

When the wound occurs in the skin by the diverse impact, results of the inflammation take places, it is characterized by redness, swelling, tenderness, and pain. When tissue is damaged, platelets adhere to exposed matrix via integrins that bind to collagen and laminin. Blood coagulation produces thrombin, which promotes platelet aggregation and granule release. The platelet granules generate an inflammatory response, leading to extravasation of white blood cells. Cytokines released by the white blood cells and platelets up-regulate integrins on macrophages, which migrate to the area of injury, and on fibroblasts and epithelial cells, which mediate wound healing and scar formation(7-9).

The experimental studies of Jawoongo have been reported previously by Eo(10) and Yi(11). However, the effect of Jawoongo plus *Rehmanniae Radix*(生地黃) has not been investigated to our knowledge.

The aim of this study is to investigate the effect of Jawoongo plus *Rehmanniae Radix*(生地黃) on the healing of incisional skin wound in rats. After inducing an inflammation on the rats, we observed the amount of Leukocyte, the level of Cortisol and CRP(C-reactive protein), and have obtained the healing effect of wound by using Jawoongo plus *Rehmanniae Radix*(生地黃).

Ⅱ. Materials and Methods

1. Materials

1) Animals

Male sprague-dawley rats with a body weight of 250-300g were maintained in an airconditioned room with lighting from 7 a.m. to p.m. The room temperature(about 23℃) and humidity(about 60%) were controlled automatically. A laboratory pellet chew (Sam-Yang Co.) and water were given freely.

The rats were adapted themselves for 2 weeks to lab circumstances before being used.

2) Herbal prescription

Most of herbs for the prescription used in this study were purchased at Dong-Eui Oriental Medicine Hospital(Pusan, Korea), and *Oleum Sesami*(胡麻油) was purchased at market. The composition of Jawoongo plus *Rehmanniae*

Radix (生地黃) is described in Table 1.

Table 1. Composition of Jawoongo plus *Rehmanniae Radix*(生地黃)

Herbs	*Scientific Name*	Dose
胡麻油	*Oleum Sesami*	100g
生地黃	*Rehmanniae Radix*	25g
當歸	*Angelicae gigantis Radix*	25g
紫草	*Lithospermi Radix*	25g
豚脂	*Adeps Suillus*	25g
蜜蠟	*Beeswax*	15g
Total		215g

2. Methods

1) Preparation of sample solution(1)

Oleum Sesami(胡麻油) was boiled for 1-2hr and *Beeswax*(蜜蠟) and Adeps Suillus(豚脂) were solved in this solution. *Angelicae gigantis Radix*(當歸) and *Lithospermi Radix*(紫草) were added and heated until these color was red-violet. And then these herbs were filtered with cotton patch.

Rehmanniae Radix(生地黃) was extracted with distilled water at 100℃ for 3hr by the extract machine. The extract was filtered through a filter paper, and concentrated through a evaporator resulting in a semifluid, and it was made into powder through the dry oven.

2) Wound creation and care

The back skin of rats was shaved under ether anesthesia. And we made an incision circular.

Rats used in experiment were divided into five groups.

Normal : Group of non-treated rats

Control : Group of skin wound and non-treated rats

Sample Ⅰ: Group of skin wound and Jawoongo applied rats

Sample Ⅱ: Group of skin wound and Jawoongo plus *Flos Lonicerae* (生地黃) applied rats

Sample Ⅲ: Group of skin wound and Madecassol® applied rats

* Gel ointment used was the commercially available Madecassol® ointment from Dong Kook Pharm. Co. LTD.(Chung-Buk, Korea)

3) Observation of wound healing procedure

After inducing wound, we took the tissue on 1st, 5th, 10th and 15th day. Every day the rats were applied to the incised site by the Jawoongo plus *Rehmanniae Radix* (生地黃) and Madecassol®, respectively.

4) Blood - gathering

We obtained the blood sample(0.6ml) from the rats on 5th, 10th and 15day and the serum had been centrifuged for 15minute(4℃, 3000rpm).

5) Measurement of Leukocyte

The number of Leukocyte was measured by the Coulter counter(model s-plus, Coulter Co, U.S.A.).

6) Measurement of Cortisol

Cortisol in the serum was measured by RIA(radioimmunoassay)method and determined by kit (DPC, America) & Gamma counter(1470 Wizard, Finland).

7) Measurement of CRP(C-reactive protein)

CRP in the serum was measured by Latex method and determined by CRP latex kit(Japan) & spectrophotometer(Hitachi 7170, Japan).

8) Dying of tissues

In this histological examination, six rats in each group were sacrificed. To observe of wound healing procedure, skin taken from rats was fixed in 4% neutral formalin, dehydrated with alcohol and then dipped into paraffin. Tissue was cut 6㎛ in thickness, was dyed with hematoxylin-eosin (H-E) and was done periodis acid Schiff(PAS) reaction. For the evaluation of the distribution of collagen fiber in the wound healing process, we used Masson's trichrome stain. and we observed inducible nitric oxide synthase(iNOS)

Ⅲ. Results

1. Leukocyte measurement

The result of Leukocyte measurement is shown in Table 2.

2. CRP(C-reactive protein) measurement

The result of CRP measurement is shown in Table 3.

3. Cortisol measurement

The result of Cortisol measurement is shownin Table 4.

Table 2. The effect of Jawoongo plus *Rehmanniae Radix*(生地黃) on the Leukocyte measurement in the skin wounded rats (M±S.E. , $\times 10^3/\mu\ell$)

Group \ Day	5	10	15
Normal	8.2±0.47		
Control	8.3±0.39	10.3±0.59	12.0±0.79
Sample I	8.7±0.26	10.2±0.30	8.5±0.26***
SampleII	7.8±0.29	10.1±0.81	9.7±0.52*
SampleIII	8.9±0.53	9.1±0.20*	8.4±0.55***

M±S.E. : Mean±Standard Error

Normal : Group of non-treated rats

Control : Group of skin wound and non-treated rats

Sample I : Group of skin wound and Jawoongo applied rats

SampleII : Group of skin wound and Jawoongo plus *Rehmanniae Radix*(生地黃) applied rats

SampleIII : Group of skin wound and Madecassol applied rats

* : Statistical significance as compared with Control (* : P < 0.05, *** : P < 0.005)

Table 3. The effect of Jawoongo plus *Rehmanniae Radix*(生地黃) on the CRP level in the skin wounded rats (M±S.E. ,㎎/dℓ)

Group \ Day	5	10	15
Normal	0.40±0.03		
Control	0.85±0.04	0.53±0.02	0.49±0.02
Sample I	0.84±0.06	0.49±0.03	0.52±0.01
SampleII	0.82±0.03	0.47±0.04	0.56±0.02*
SampleIII	0.83±0.05	0.54±0.04	0.51±0.03

Other legends are same as Table 2

* : Statistical significance as compared with Control (* : P < 0.01)

Table 4. The effect of Jawoongo plus *Rehmanniae Radix*(生地黃) on the Cortisol level in the skin wounded rats (M±S.E. , ㎍/dℓ)

Group \ Day	5	10	15
Normal	0.05±0.01		
Control	0.17±0.02	0.26±0.01	0.20±0.01
Sample I	0.14±0.01	0.21±0.02*	0.24±0.01**
Sample II	0.20±0.02	0.13±0.02***	0.25±0.02*
Sample III	0.48±0.03***	0.46±0.03***	0.06±0.04***

Other legends are same as Table 2

* : Statistical significance as compared with Control (* : P < 0.05, ** : P< 0.01, *** : P < 0.005)

4. Wound area Measurement

The wound area was traced and the square size was calculated by an image analyzer. Data are expressed as % of the initial wound area which was measured on the day following wound. The result of wound area measurement is shown in Table 5

Table 5. The effect of Jawoongo plus *Rehmanniae Radix*(生地黃) on the size of incision and the rate of reduction (×mm)

Group \ Day	1	5	10	15
Control	10.55	5.57 (47.2%)[a)]	2.16 (61.2%)[b)]	0.84 (61.5%)[c)]
Sample I	11.18	6.92 (38.1%)	2.11 (69.5%)	0.27 (87.2%)
Sample II	12.10	8.59 (29.0%)	1.98 (76.9%)	1.55 (21.7%)
Sample III	11.43	7.23 (36.8%)	4.68 (35.3%)	1.08 (76.9%)

Other legends are same as Table 2

The rate of reduction(%)

a) : (1day-5day)/1day

b) : (5day-10day) / 5day

c) : (10day-15day)/10day

5. Histological evaluation

Figure 1-6 show the results for the histologic evaluation of wound healing process.

Angiogenesis, epithelial elongation and differentiation is showed higher value in the Jawoongo group, Jawoongo plus *Rehmanniae Radix*(生地黃) group but lower or equal value in Madecassol® group than control group.

The thickness of necrotic layer in the wound revealed lower values in the all experimental groups than control group

In the thickness of granulation layer, Madecassol® group showed lower values than control group but the other groups showed higher values than control groups.

In the length of subcutaneous collagenous scar tissue, all experimental group showed similar to lower values on 5 days after wound, but Madecassol® group and Jawoongo plus *Rehmanniae Radix*(生地黃) group showed higher values than control groups on 15 days after wound.

On the observation of collagen fiber by the Masson's trichrome stain, Jawoongo plus *Rehmanniae Radix*(生地黃) group showed higher values than Jawoongo group in the granulation layer or collagenous scar tissue on 10 days after wound.

On the immunohistoiogical observation of iNOS, all experimental groups showed higher reaction than control group in the epithelial cell and scab layer on the 5 days after wound

Fig. 1. Histoiogical evalution based on the scores of wound areas

Fig. 2. Histological measurment of wound areas

Fig. 3. Back skin of rat showing excisional wound in the control (A), sample I (B), sample II (C) and sample III (D) on 10 days after wound. H-E staining. ×200.

Fig. 4. Back skin of rat showing excisional wound in the control (A), sample I (B), sample II (C) and sample III (D) on 5 days after wound. PAS reaction. ×200.

Fig. 5. Back skin of rat showing excisional wound in the control (A), sample I (B), sample II (C) and sample III (D) on 10 days after wound. Masson's trichrome staining. ×200.

Fig. 6. Back skin of rat showing excisional wound in the control (A), sample I (B), sample II (C) and sample III (D) on 5 days after wound. anti-iNOS antibody staining. × 200.

Ⅳ. Discussion

The application of herbal medicines dates back to the beginning of civilization. Interestingly, herbal medicines are still routinely used by many of world's population. Further, herbal medicines has been used for the improvement of diseases in Asian countries for centuries. Over time, information has accumulated pertaining to the practical use of herbs, such as their efficacy and adverse reactions.

Oriental medicine views the body as an Um (陰), Yang(陽) system and emphasizes abnormality in the balance or flow of Ki(氣) and Hyul(血) as the sources of disease. Thus, the basic principle of the traditional Oriental medicine therapy is to regulate the homeostasis of the whole body and to normalize the physical disorders. The method for remedy the diseases in the oriental medicine is the administration of herbs with a combination of a number of ingredients. But some herbal medicines included Jawoongo has been treated by spreading on the skin.

Jawoongo, a traditional oriental medicine ointment, have been used for patients withcutaneous diseases(12-14). It is a oriental herbal medicine formula consisting of four ingredients, derived from Yungigo supplement with *Adeps Suillus* (豚脂). Yungigo was originally prescribed by Jin(5) for scabby scalp in A.D. 1555 and has been widely applied in seborrhea, fracture, abrasion, bruise, frostbite and scald, etc.(1, 3, 4, 6, 9, 15, 16).

Doctors have applied Jawoongo for treating eczema, neurodermatitis and impetigo, etc. by promoting blood flow(活血), dispersing wind(散風) and moistening(潤燥)(1-4, 17-19).

Ingredient of Jawoongo plus *Rehmanniae Radix* (生地黃) are as follow.

Lithospermi Radix(紫草) is bitter and moderate cold, and is channelled into liver, heart and pericardium meridians with the effect of removing heat from blood(淸熱凉血), promoting

blood flow(活血), detoxicating(解毒), promoting eruption(透疹), removing smallpox and erysipelas.(14, 20).

Angelicae gigantis Radix(當歸) in this prescription has sweet and hot flavor and warm property, and is channelled into liver, heart and spleen meridians with the effect of tonifing the blood(補血), regulating menstruation(調經), alleviating pain(止痛), and is administrated to suppurative infection on body surface and abscess.(14, 20).

Oleum Sesami(胡麻油) is sweet flavor and even property, and is channelled into liver, spleen, lung and kidney meridians with the effect of nourishing Um of the liver and kidney (滋養肝腎), activating intestine by moistening(潤燥活腸), and is used as a basic ingredients of making an ointment.(14, 20).

Adeps Suillus(豚脂) is sweet flavor and moderate cold and has the effect of moistening (潤燥), tonifing deficiency(補虛) and detoxicating(解毒)(21).

Rehmanniae Radix(生地黃) has sweet flavor and cold property, and is channelled into heart, liver and kidney meridians with the effect of removing heat from the blood(淸熱凉血), promote secretion of body fluid(生津), and quenching with thirst(止渴), and used in treatment of bleeding, fever, and urticaria on body surface, etc. (14, 20).

There have been many experimental studies on the wound healing. An(22) reported the effect of Sagunjatang extract and Sagunjatang added Radix Astragali(黃芪) extract on the granulation tissues. Eo(10) reported the effect of Jawoongo on the artificial wound on rat skin.

Healing proceeds temporally in three phases : substrate, proliferative, and remodeling. The initial substrate phase, encompassing the first 3 to 4 days after wounding, is so named because the cellular and other interactions lead to preparation for subsequent events. During this phase vascular and inflammatory components prevail(vascular clotting in the severed vessels ; leukocyte and macrophage chemotaxis into the area to ingest bacteria, debride the wound, and degrade collagen). The proliferative phase (10 to 14 days after wounding) results in regeneration of epidermis, neoangiogenesis, and proliferation of fibroblasts with increased collagen synthesis and closure of the skin defect. The final remodeling phase takes place over 6 to 12 months, during which time a more stable form of collagen is laid down to form a scar of progressively increasing tensile strength(8, 9, 23).

According to the present study, normal value of Leukocyte is $8.2\pm0.47(\times10^3/\mu\ell)$ and after 5day, 10day, 15day, Control is 8.3 ± 0.39, 10.3 ± 0.59, 12.0 ± 0.79, Sample I is 8.7 ± 0.26, 10.2 ± 0.30, 8.5 ± 0.26, SampleII is 7.8 ± 0.29, 10.1 ± 0.81, 9.7 ± 0.52, SampleIII is 8.9 ± 0.53, 9.1 ± 0.20, 8.4 ± 0.55, respectively. The value of SampleII was decreased compared with that of Control on 15days after wound.

Normal value of CRP is 0.40 ± 0.03(㎎/dℓ) and after 5day, 10day, 15day, Control is 0.85 ± 0.04, 0.53 ± 0.02, 0.49 ± 0.02, Sample I is 0.84 ± 0.06, 0.49 ± 0.03, 0.52 ± 0.01, SampleII is 0.82 ± 0.03, 0.47 ± 0.04, 0.56 ± 0.02, SampleIII is 0.83 ± 0.05, 0.54 ± 0.04, 0.51 ± 0.03, respectively. The value of SampleII was increased compared with that of

Control on 15day after wound.

Normal value of Cortisol is 0.05±0.01(㎍/dℓ) and after 5day, 10day, 15day, Control is 0.17± 0.02, 0.26±0.01, 0.20±0.01, Sample I is 0.14± 0.01, 0.21±0.02, 0.24±0.01, SampleII is 0.20± 0.02, 0.13±0.02, 0.25±0.02, SampleIII is 0.48± 0.03, 0.46±0.03, 0.06±0.004, respectively. The value of SampleII were significantly decreased compared with those of Control of 10 day and 15day, whereas, the value of SampleIII were significantly increased compared with those of Control of 5day and 10 day, and decreased compared with that of 15day.

We observed the size of incision every 1day, 5day, 10day, 15day. Control is 10.55, 5.57(47.2), 2.16(61.2), 0.84(61.5), Sample I is 11.18, 6.92(38.1), 2.11(69.5), 0.27(87.2), SampleII is 12.10, 8.59(29.0), 1.98(76.9), 1.55(21.7) and SampleIII is 11.43, 7.23(36.8), 4.68(35.3), 1.08(76.9), respectively. The rate of reduction of Sample II after 10day is higher than that of Control group with statistical significance. But the rate of reduction of Control is higher than that of other group with no statistical significance in 5day.

According to histologicl evaluation, angiogenesis, epithelial elongation and differentiation is showed higher value in the Jawoongo group, Jawoongo plus *Rehmanniae Radix*(生地黃) group. The thickness of necrotic layer in the wound revealed lower values in the all experimental groups than control group. In the thickness of granulation layer, Madecassol® group showed lower values than control group but the other groups showed higher values than control groups. In the length of subcutaneous collagenous tissue, all experimental group showed similar to lower values on 5 days after wound, but Madecassol® group and Jawoongo plus *Rehmanniae Radix*(生地黃) group showed higher values than control groups on 15 days after wound.

On the observation of collagen fiber, Jawoongo plus *Rehmanniae Radix*(生地黃) group showed higher values than Jawoongo group in the granulation layer or collagenous scar tissue on 10 days after wound.

On the immunohistological observation of iNOS, all experimental groups showed higher reaction than control group in the epithelial cell and scab layer on the 5 days after wound

Skin wound healing is a complex process characterized by reepithelization and restoration of the underlying connective tissue. During this process, keratinocytes, endothelial cells, fibroblasts, and inflammatory cells proliferate and/or migrate to the site of injury, interacting with extracellular matrices. In the healing process, angiogenesis, granulation tissue formation and reepithelization are essential process histologically and wound spasm is used for the histologic marker and collagen fibers help connective tissue reconstruction(24-27).

From this study, we have identified the effectiveness of Jawoongo plus *Rehmanniae Radix*(生地黃) as oriental medicine in wound healing. In comparison with Jawoongo alone, addition of *Rehmanniae Radix*(生地黃) have showed some positive effects in wound healing but not show statistical significance. The problem if the error comes from preparation step or other step remains unsolved and further

studies are required. But from this experiment, the effect of oriental ointment was proved in some degree. And detailed approach for more effective and stable ointment should be continued in the future.

4. In the analysis of size of incision, the reduction rate of Sample II after 10day is higher than that of Control group with statistical significance. But the rate of reduction of Control is higher than that of other group with no statistical significance in 5day.

V. Conclusion

To evaluate the effect of Jawoongo plus *Rehmanniae Radix*(生地黃) in the process of wound healing, we performed the leukocyte measurement, CRP measurement, cortisol measurement and tissue stain with hematotoxylin-eosin(H-E). The results were as followed.

1. In the leukocyte measurement, Sample II was decreased compared with Control on 15days.

2. In the CRP measurement, Sample III were increased compared with Control on 15days, but other parts were showed no stastical significance.

3. In the cortisol measurement, the value of SampleII were significantly decreased compared with those of Control of 10 day and 15day, whereas, the value of SampleIII were significantly increased compared with those of Control of 5day and 10day, and decreased compared with that of 15day.

These results imply that Jawoongo plus *Rehmanniae Radix*(生地黃) has effect of wound healing, but has little statistical significance comparing with Jawoongo.

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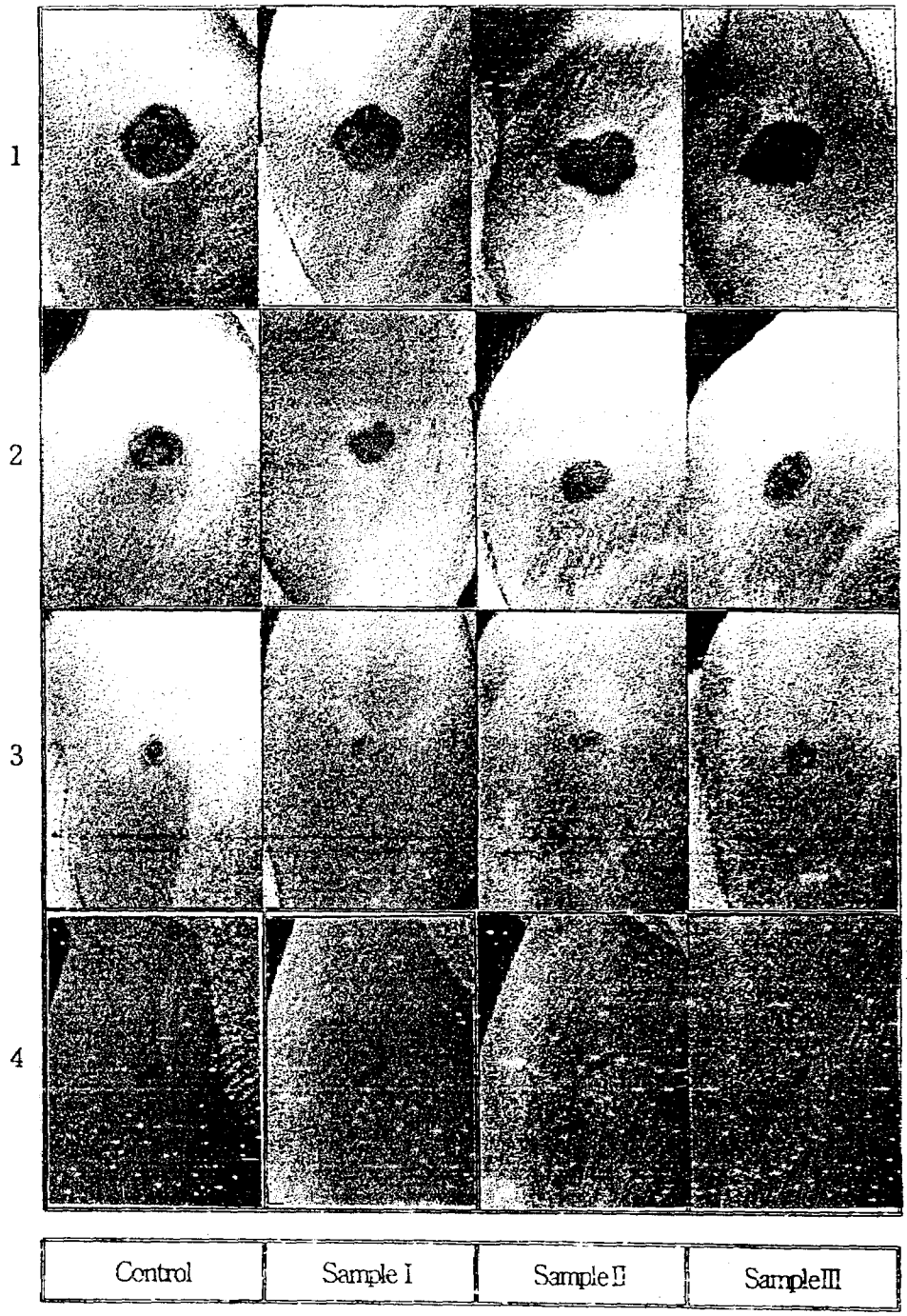

1
2
3
4
Control
Sample I
Sample II
SampleIII

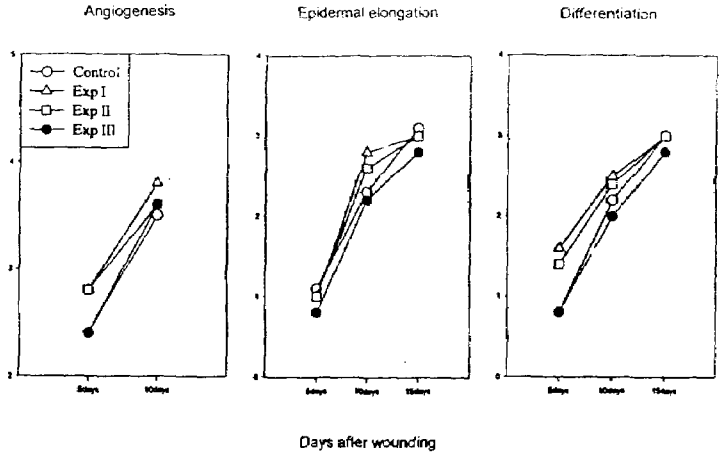
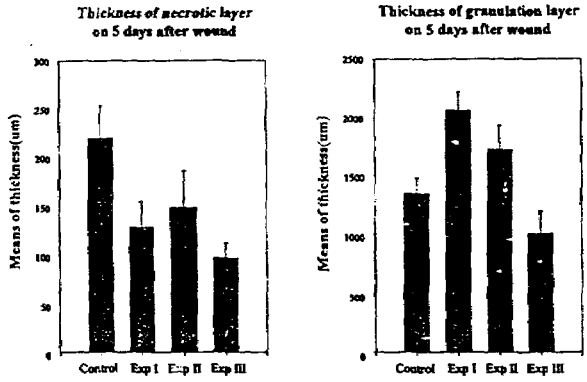

Angiogenesis
Epidermal elongation
Differentiation
Control
Exp I
Exp II
Exp III
Days after wounding

Fig. 1


Thickness of necrotic layer on 5 days after wound
Thickness of granulation layer on 5 days after wound
Means of thickness(um)
Control
Exp I
Exp II
Exp III

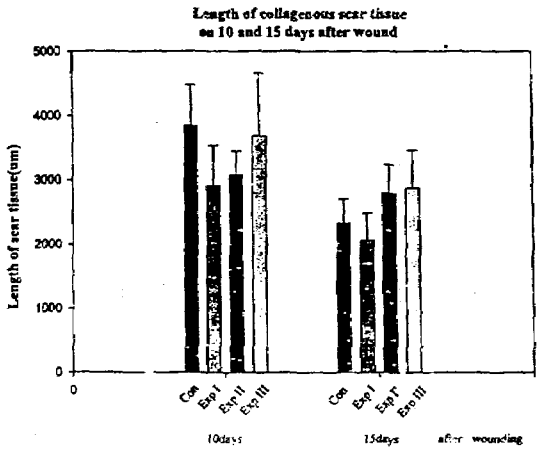

Length of collagenous scar tissue on 10 and 15 days after wound
Length of scar tissue(um)
10days
15days
after wounding

Fig. 2

A
B
C
D

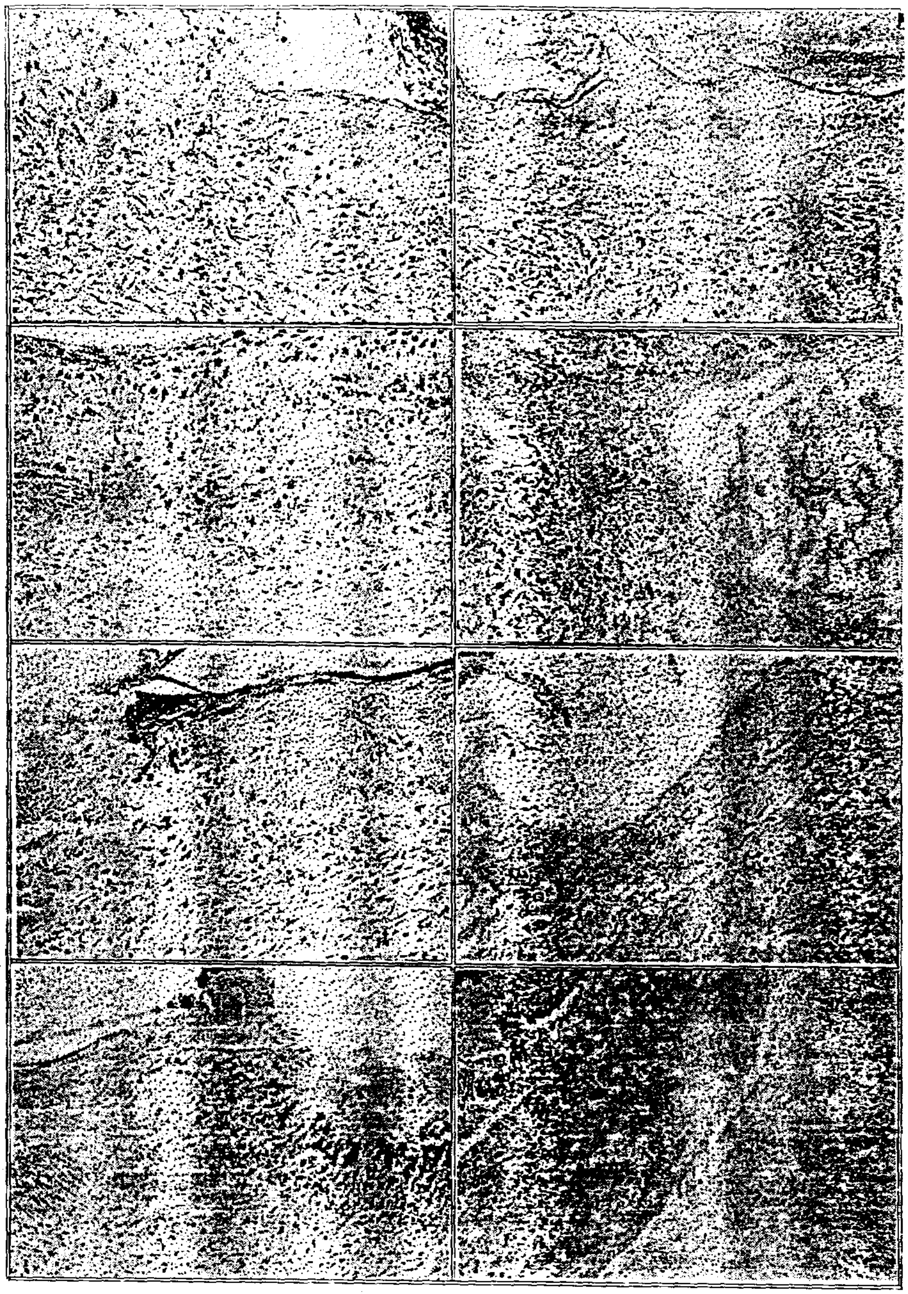


Fig. 3	Fig. 4

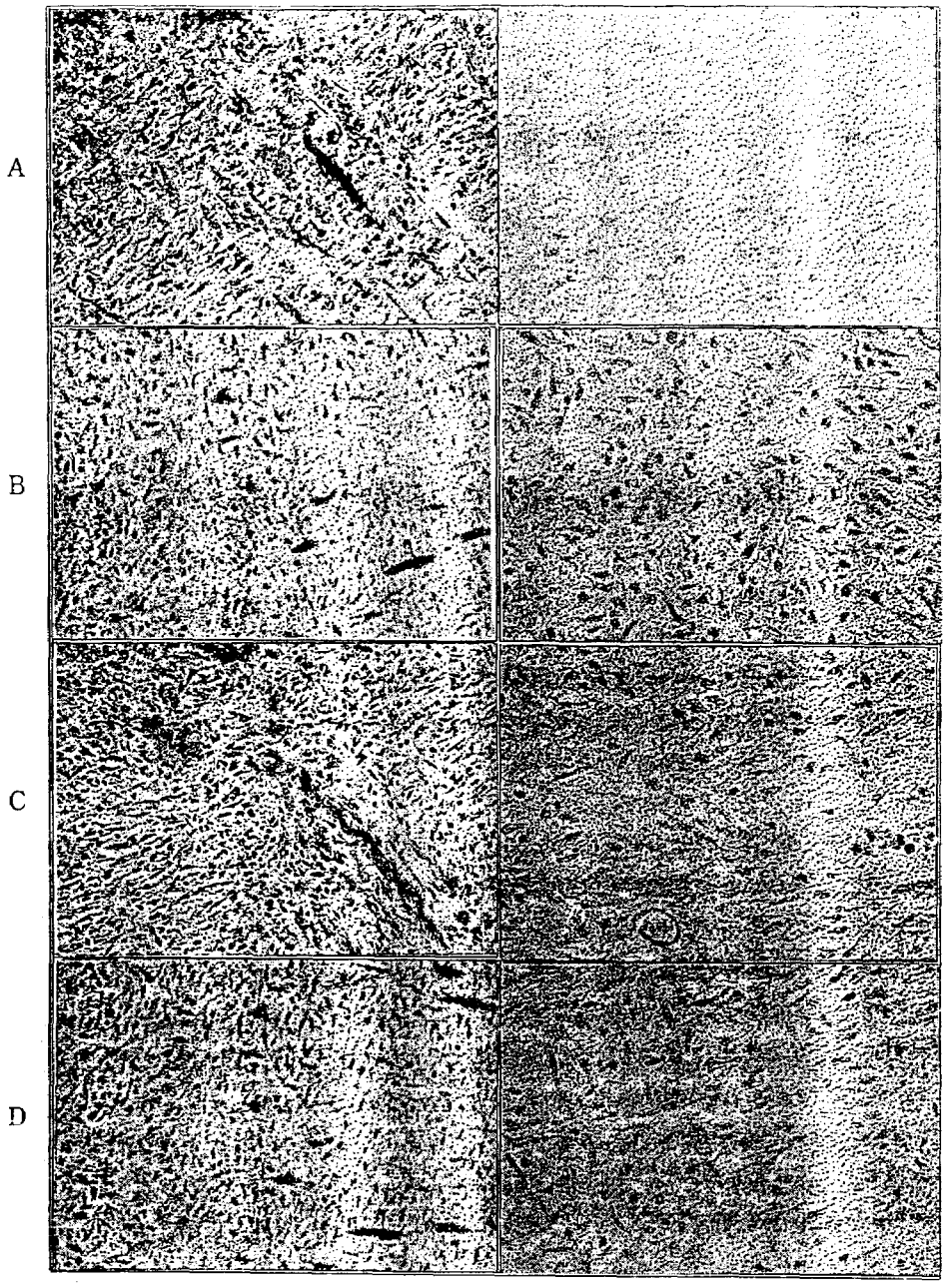


Fig. 5	Fig. 6