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The Effect of Curcumin on the Acute Wound Healing of Mice

Armansjah Dara Sjahruddin[1], Anis IrawanAnwar[1], Farida Tabri[1], Khairuddin Djawad[1], Dasril Daud[2], Gemini Alam[3]

[1]Dermatovenereology Department, Medical Faculty Hasanuddin University, Makassar, South Sulawesi, Indonesia
[2]Pediatric Department, Medical Faculty Hasanuddin University, Makassar, South Sulawesi, Indonesia
[3]Pharmacy Faculty, Hasanuddin University, Makassar, South Sulawesi, Indonesia

Email address:

ariedara@yahoo.com (A. D. Sjahruddin), anisianwar@yahoo.co.id (A. I. Anwar), farida_tabri@yahoo.com (F. Tabri), duddindj@gmail.com (K. Djawad), ikkkfkuh@yahoo.co.id (G. Alam), drdasril@gmail.com (D. Daud)

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Abstract: Background: The study aimed to compare the effectiveness of curcumin 0.5% and 5% by Natrium Chloride (NaCl) 0.9% in the acute wound healing of mice. Methods: This study was conducted at the Animal Laboratory and at the Department of Anatomical Pathology, Medical Faculty Hasanuddin University in Makassar, by using an experimental study. The samples consisted of 30 mice observed by the change of clinical and histopathological manifestations. Result: The study reveal that there was no significant difference between the application of curcumin 5% and Natrium Chloride 0.9% in the healing wound. After seven days the length of significant reepithelization was p=0.026 between curcumin 0.5% and Natrium Chloride 0.9%. After the seventh day of treatment the density of polymorpho nuclear (PMN) and macrophages was not significant ($p<0.05$) in all three groups. Statistically, the thickness of fibroblast was significant, between Natrium Chloride 0.9% and curcumin 0.5% (p=0.049), curcumin 5% (p=0.006) after the treatment on day seven. Conclusions: The use of application topical curcumin is not better than the NaCl 0.9% in acute wound healing in mice.

Keywords: Clinical Manifestation, Curcumin, Histopathology, Natrium Chloride, Wound Healing

1. Introduction

Skin is the most extensive organ and has many diverse functions include protection, thermoregulation, sensation, wound healing and regeneration, as well as the physical appearance of a person.(1) If there is an injury to the skin, it will disturb the anatomical structures and functions as a result of pathological processes.(2)

Definition of injury is a damage to the skin continuity, tissues in the body both internal and external, causing traumatic effects.(3) Acute and chronic wounds have similarities and differences in physiological terms. Acute wounds healing after passing through four phases of wound healing, namely hemostasis, inflammation, proliferation, and remodeling. In contrast, chronic wounds have the same initial phase but has a longer duration of the phases of inflammation, proliferation, and remodeling that can lead to the occurrence of tissue fibrosis, leaving cicatrix or unhealed ulcer.(4)

Turmeric or *Curcuma longa Linn* (synonym of *Curcuma domestica Val*) from Zingiberaceae family is one of the important types of medicinal plants and their use quite a lot in Indonesia.(5) On traditional medicine, turmeric is used as an anti-inflammatory, which curcumin is concluded as balancer between pro and anti-inflammatory mediators, as well as antiseptic, anti-irittant, and anorexia. Curcuminoid, the active ingredient in turmeric that has a broad spectrum of biological activities. Besides, turmeric has significant antibacterial activity on *Bacillus cereus*, *Staphyllococcus aureus* and *Pseudomonas aeruginosa*. Provision of turmeric is also recognized as the appropriate therapy in wound healing.(6)

Wound healing process that aims to speed healing, is important to avoid infection in the wound, the longer duration of the phases of inflammation, proliferation, and remodeling resulting in tissue fibrosis and ulcers. Based on the statements above, it raised the interest to find out if curcumin has efficacy when administered topically to acute wound healing process in the hope of speeding up the duration of the third stage of wound healing when compared with the use of Natrium Chloride (NaCl) 0.9% as wet dressings.

2. Materials and Methods

This study is an animal experimental design to compare the effectiveness of topical curcumin 0.5% and 5% with NaCl 0.9% as wet dressing in mice within 3 and 7 days with a once daily application (0,2 ml topical). The curcumin concentration of 0.5% and 5% obtained by mixing it with ethanol 96% so that the form of a solution. The study was conducted in February - March 2015 in Animal Laboratory and Department of Anatomical Pathology, Medical Faculty, Hasanuddin University Makassar. After receiving approval from the animal ethics committee, we obtained total sample is 30 albino strain of white mice of either sex, healthy, aged 10-12 weeks, and weight 20-30 grams. The sample was randomly selected a total of 30 samples to comply with the number of samples.

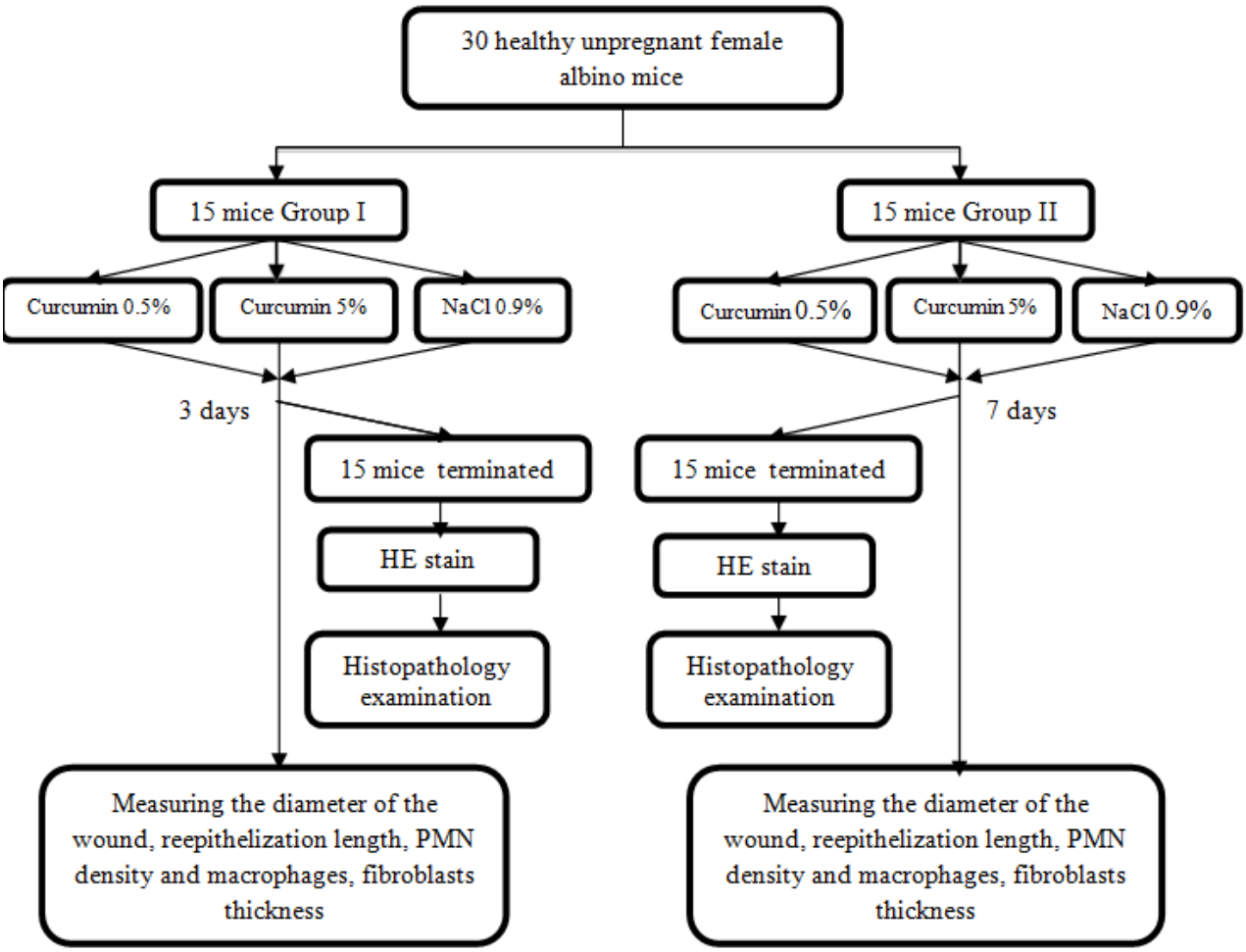

Figure 1. *Study flow scheme.*

We split into two groups observation on days 3 and 7, is based on that process reepithelization started on day 3, and epithelization in wet, moist, and dry wounds was completed by days 7.[6]

Collected data were edited, tabulated and incorporated into a computer program, and then conducted a descriptive and analytical analysis. Results of the analysis will be presented in tables or graphs accompanied by explanations. Data analysis was performed using SPSS version 21. Statistical test was performed using ANOVA followed by t-test, independent test, with significance level $p < 0.05$.

3. Results

The data we obtained in this study are shown in the table below:

Table 1. *The diameter of the wound after treatment day 3.*

Wound Diameter	**Curcumin 0.5%**		**Curcumin 5%**		**NaCl 0.9%**	
(mm)	SBefore	After	Before	After	Before	After
	(n=5)	(n=5)	(n=5)	(n=5)	(n=5)	(n=5)
Mean	5	4.20	5	3.8	5	3.6
Median	5	4	5	4	5	4
Sd	0	0.45	0	0.45	0	0.55
Min-Max	5-5	4-5	5-5	3-4	5-5	3-4
p	0.016		0.04		0.005	

T_4=4.00, p=0.016(p<0.05), T_4=6.00, p=0.04(p<0.05), T_4=5.72, p=0.005(p<0.01)

Note : T_4 = T test paired sample ; Sd = Standard deviation

There was a significant difference in the administration of curcumin 0.5%, curcumin 5% and NaCl 0.9% on the diameter of the wound before and after 3 days, which is characterized by reduced size of the diameter of the wound

Table 2. *Comparison of the difference in diameter of the wound after treatment day 3.*

Difference in diameter wound	Curcumin 0.5%	Curcumin 5%	NaCl 0.9%
(mm)	(n=5)	(n=5)	(n=5)
Mean	0.8	1.2	1.4
Median	1.0	1.0	1.0
Sd	0.44	0.44	0.54
Min-Max	0-1	1-2	1-2

F_2= 2.00, p=0.178 (p>0.05)
Note : F_2 = ANNOVA test; Sd= Standard deviation

Table 2 above shows a comparison of the difference between the diameter of the wound at day 3 of treatment by administration of curcumin 0.5%, curcumin 5% and NaCl 0.9%, showed no significant difference.

Table 3. *The diameter of the wound after treatment day 7.*

Wound Diameter	Curcumin 0.5%		Curcumin 5%		NaCl 0.9%	
(mm)	Before (n=5)	After (n=5)	Before (n=5)	After (n=5)	Before (n=5)	After (n=5)
Mean	5	5.40	5	2.8	5	2.5
Median	5	5	5	3	5	2.5
Sd	0	1.14	0	0.84	0	0.50
Min-Max	5-5	4-7	5-5	2-4	5-5	2-3
p	0.477		0.004		0.000	

T_4=0.784, p=0.477 (p>0.05) T_4=5.89, p=0.004(p<0.05) T_4=11.18, p=0.000(p<0.05)
Note : T_4 = T test paired sample ; Sd = Standard deviation

Administration of curcumin 0.5% showed no significant difference before and after treatment, but the administration of curcumin 5% and NaCl 0.9% on the diameter of the wound for 7 days reveal any significant differences before and after treatment. It is characterized by the reduced size of the diameter of the wound at each awarding curcumin 5% and NaCl 0.9%.

Table 4. *Comparison of the difference in diameter of the wound after treatment day 7.*

Difference in wound diameter	Curcumin 5%	NaCl 0.9%
(mm)	(n=5)	(n=5)
Mean	2.8	2.5
Median	2.0	2.5
Sd	0.84	0.5
Min-Max	1-3	2-3

T_8=1.210, p=0.303 (p>0.05)
Note : T_8 = Independent Test; Sd= Standard deviation

From the comparison of the difference in diameter of the wound on day 7 of treatment with curcumin administration and NaCl 0.9% to 5%, showed no significant differences.

Table 5. *Reepithelization after treatment day 3.*

Microscopic wound length	Curcumin 0,5	Curcumin 5%	NaCl 0.9%
(µm)	(n=2)	(n=2)	(n=2)
Mean	191.5	191	236
Median	191.5	191	236
Sd	54.45	18.39	8.49
Min-Max	152-230	178-204	230-242

F_2= 1.187, p=0.417(p>0.05)
Note : F_2 = ANNOVA test; Sd= Standard deviation

Table 5 above showed no significant differences the reepithelization wound healing after treatment days 3 with curcumin 0.5%, curcumin 5%, and NaCl 0.9%.

Table 6. *Reepithelization length after treatment day 7.*

Reepithelization length	Curcumin 0.5%	Curcumin 5%	NaCl 0.9%
(µm)	(n=4)	(n=4)	(n=5)
Mean	178.5*	102	69*
Median	172	95.5	64
Sd	37.82	69.63	40.98
Min-Max	140-230	26-191	26-128

F_2= 5.35, p=0.026(<0.05)
Note : F_2 = ANNOVA test; Sd= Standard deviation
Post Hoc Bonferroni * p=0.026 (p<0.05)

Table 6 above showed the reepithelization wound healing after 7 days of treatment found significant differences. In this case that showed the significant difference in the group that received NaCl 0.9% is the shortest length of the wound compared with two other treatments.

Tabel 7. *PMN and macrophages density in wound healing after treatment day 3.*

PMN and macrophages density	Curcumin 0.5%	Curcumin 5%	NaCl 0.9%
(%)	(n=4)	(n=4)	(n=5)
Mean	62.6*	63.2*	35.8*
Median	60	63	30
Sd	8.57	9.42	19.99
Min-Max	53-73	54-75	13-60

F_2=6,540, p=0,012 (p<0.05)
Post Hoc Bonferroni *p=0,028 (p<0.05), p=0,023 (p<0.05)
Note : F_2 = ANNOVA test; Sd= Standard deviation

Table 7 above is visible density of PMN and macrophages wound healing after day 3 of treatment there appears to be significant differences among the 3 treatment groups. In this case the density of the smallest PMN and macrophages found in the group of NaCl 0.9% compared with the two other groups.

Tabel 8. *PMN and macrophages density in wound healing after treatment day 7.*

PMN and macrophages density	Curcumin 0.5%	Curcumin 5%	NaCl 0.9%
(%)	(n=5)	(n=5)	(n=5)
Mean	52.6	32.4	62.8
Median	43	27	70
Sd	21.65	19.57	18.46
Min-Max	33-87	8-57	43-80

F_2=3,013, p=0,087 (p>0.05)
Note : F_2 = ANNOVA test; Sd= Standard deviation

Table 8 showed no significant differences among the three groups that the density of PMN and macrophages of wound healing after 7 days.

Tabel 9. *The thickness of fibroblasts in wound healing after treatment day 3.*

Fibroblast length	Curcumin 0.5%	Curcumin 5%	NaCl 0.9%
(µm)	(n=2)	(n=2)	(n=2)
Mean	34	28	19
Median	34	28	19
Sd	4.25	4.25	0
Min-Max	31-37	25-31	19-19

F_2=9,500, p=0.05 (p>0.05)
Note : F_2 = ANNOVA test; Sd= Standard deviation

From the table above it can be seen that the thickness of fibroblasts in wound healing after treatment days 3, there are no significant differences among the three groups.

Tabel 10. *The thickness of fibroblasts in wound healing after treatment day 7.*

Fibroblast length	Curcumin 0.5%	Curcumin 5%	NaCl 0.9%
(µm)	(n=4)	(n=4)	(n=5)
Mean	23.25*	9*	28.6*
Median	25	9	25
Sd	8.01	3.47	8.05
Min-Max	12-31	6-12	19-37

F_2=9.068, p=0.006 (p<0.05)
Post Hoc Bonferroni * p=0.049 (p<0.05), p=0.006 (p<0.05)
Note : F_2 = ANNOVA test; Sd= Standard deviation

Table 10 above showed the thickness of fibroblasts in wound healing after treatment day 7 found a significant difference between curcumin 0.5% with NaCl 0.9%. Similarly, curcumin 5% with NaCl 0.9% which the biggest fibroblasts thickness at NaCl 0.9% group.

4. Discussion

The results from wound diameter analysis in wound healing, showed a significant difference between the mean diameter macroscopic lesion before and after treatment in all three groups after 3 days (p <0.05), although visible under macroscopic wound diameter are best found in NaCl 0.9% group (p= 0.005). Followed in the curcumin 0.5% group (p= 0.016) and the last at curcumin 5% group (p= 0.04). Statistical analysis compared which is better than the diameter difference between the three groups wound after 3 days of treatment, showed no significant difference (p= 0.178) This is according to research conducted by Purohit et al, that curcumin has the effect of therapy in wound healing.[6]

Comparison of the mean diameter macroscopic lesion before and after treatment in all three groups after 7 days, only at 5% curcumin (p = 0.004) and NaCl 0.9% (p = 0.000) that there are significant differences. A possibility that this could be due to an infection in curcumin 0.5% group (P = 0.477). If viewed from the mean difference in diameter wound macroscopically there is no significant difference between groups curcumin 5% and NaCl 0.9%.

If we look further, we compare the diameter of the wound after treatment on day 3 between curcumin 5% (mean = 3,8mm) NaCl 0.9% (mean = 3,6mm) and at day 7 between curcumin 5% (mean = 2,8mm) NaCl 0.9% (mean = 2.5 mm) is appropriate that the results of curcumin administration in wound healing can heal wounds, but not better than NaCl 0.9%.

Analysis of reepithelization in wound healing, based on data from Table 5 and Table 6 reepithelization most value are those of curcumin 5% (191 µm), curcumin 0.5% (191.5 µm) and 0.9% NaCl (236 µm). But statistically, no significant differences found reepitelisasi length obtained from long injury, after treatment day 3 in all three groups (p = 0.417). Reepithelization after treatment day 7 (Table 6) showed a significant difference between the mean curcumin 0.5% (178 µm) and a mean of NaCl 0.9% (69 µm) (p = 0.027), and compared with curcumin 0, 5%. In study conducted by Purohit et al which examined the effects of wound healing using of *Curcuma longa* (Turmeric) rhizomes, are used for wound healed, it possesses antibacterial, anti-inflammatory, anti-allergic properties.[6]

If we look further, and we compare statistical data the reepithelization of wound healing after treatment on day 3 and day 7 seems there is a tendency smaller length value lesions (greater length reepithelization Table 7 and 8). It showed after treatment day 7, NaCl 0.9% showed better results, in terms of reepithelization.

Analysis of PMN and macrophages density in wound healing, based on data from the three groups of the distribution of the density of PMN and macrophages after treatment on day 3 obtained a significant difference between curcumin 0.5% (62.6) with NaCl 0.9% (35.8) (p= 0.028) and curcumin 5% (63.2) with NaCl 0.9% (p= 0.023).

In contrast to the three groups of the distribution of the density of PMN and macrophages after treatment day 7 curcumin 0.5% (52.6) curcumin 5% (32.4) and NaCl 0.9% (62.8) is not found significant difference, although it appears that the percentage of the density of most higher categories in NaCl 0.9% and the lowest at curcumin 5%group. Prevention of wound infection can guarantee a normal proliferation of tissue cells to cover the wound.[6] And the same thing happens to the research conducted by Mani, that the density of PMN and macrophages many categories highest in NaCl 0.9% group (100%) in acute wound healing in mice.[7].In the group NaCl 0.9% were found to foci of bacterial infection that PMN and macrophages in significant amounts phagocytes bacteria.[7] This may be caused by environmental factors such as the condition of the mice cages or host factors such as the

behavior of mice after the wound was made.[8] Sodium chloride has the effect of inhibiting the growth of bacteria in high concentrations of over 20 g / L. However, at low concentrations, NaCl in the water phase can increase the growth of bacteria.[8, 9,10] Sodium chloride 0.9% containing 9 grams of salt per liter. This causes the growth of bacteria in the group of mice given NaCl 0.9% wet dressings.[8,11,12]

If we look further, we compare statistical data density of PMN and macrophages wound healing after treatment on day 3 appears PMN and macrophage density value in the delivery of NaCl 0.9% slower, but at day 7 PMN and macrophage density values the provision of NaCl 0.9% gave similar results by administering curcumin and curcumin 0.5% to 5%, and the value of the density of PMN and macrophages to the administration of NaCl 0.9 and a rising trend clearly visible.

Analysis of fibroblasts thickness in wound healing similarly, in table 12 the value of the thickness of fibroblasts curcumin 0.5 % (mean = 34μm) curcumin 5% (mean = 28μm) NaCl 0.9% (mean = 19μm) showed no significant differences in the thickness of the fibroblasts in the three groups after treatment day 3 (p= 0.05). While the thickness of fibroblasts after treatment day 7 there is a significant difference between curcumin 0.5% (mean = 23.23μm) with NaCl 0.9% (mean = 28.6μm) (p= 0.49) and curcumin 5% (mean = 9μm) with NaCl 0.9% (mean = 28.6μm) (p= 0.06). It is appropriate that the fibroblasts begin to decline at day 7 marks the proliferative phase towards remodeling.[11, 12] Wound healing is a complex biological process and dynamic, which consists of 3 phases which inflammation, tissue formation and remodeling.[13] Normal wound healing requires good circulation, nutrition, and immune status. Generally necessary process for 3-14 days for complete recovery.[14] In the process reepithelization, fibroblasts restore network stability by producing collagen, fibronectin, elastin, and peptidoglycan. The formation of the matrix fibers will cause a significant reduction in wound size.[15]

If we look further, if we compare statistics the thickness of fibroblasts on wound healing after treatment on day 3 and day 7 seems there is a tendency smaller thickness value fibroblasts NaCl 0.9% lower on day 3, but on the day to 7 thickness values of fibroblasts in the provision of NaCl 0.9% showed better results.

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