Original Article

Comparison of Effect of pH Modulation on Wound Healing with Topical Application of Citric Acid Versus Superoxide Ions

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Abstract

Background: Wound healing is a dynamic process involving tissue repair and regeneration. Nonhealing and chronic wounds are a significant health problem that many patients all over the world are suffering from. Proper wound care is hence very important. Wound dressings have undergone continuous and significant changes over the time period. Optimal dressing should ensure a moist wound bed, help drainage, remove debris, and be anti-allergic and without immunogenicity. **Objectives:** The objective of the study is compare the effect of pH modulation on wound healing with topical application of citric acid versus superoxide ions. The aim is to study the efficacy and safety of citric acid versus superoxide ions in the prevention and control of infection and their effect on wound healing in similar wound types. **Materials and Methods:** We conducted randomized, prospective comparative study in a total of 100 patients admitted at Guru Nanak Dev Hospital, attached to Government Medical College, Amritsar. The patients were divided into two groups: Group A where wound management was done using superoxide ions and Group B where citric acid was used. A standard grading was done in terms of a decrease in wound size, an increase in granulation tissue, and a reduction in wound discharge. **Results:** The wounds treated with citric acid showed an average reduction in wound size of 73.43% by the 14th day as compared to 66.52% in the control group. The difference seen in the average reduction of wound size was statistically significant (P = 0.032). The wounds treated by citric acid application showed an average increase in granulation tissue of 56.66% as compared to 50.87% in the wounds treated by superoxide ions. The average hospital stay in patients of Group B was comparatively less than that of patients in Group A. **Conclusion:** Citric acid is safe and effective in all types of wound management and gives better efficacy and faster response as compared to superoxide ions. Citric acid promotes wound healing by the formation of granulation tissue and fibroblast proliferation.

Keywords: *Citric acid, superoxide ions, wounds*

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Introduction

Wounds and their management form a crucial part in the practice of surgery. A wound is a break in the continuity of epithelium from violence or trauma.[1] Stimuli that can break the skin continuity can be external or internal, as well as physical, chemical, electric, or thermal.[2]

Various distinct and overlapping phases are involved in wound healing[1] after the initial hemostasis, inflammatory phase ensues which mainly consists of cellular cleaning of the wound by macrophages. The proliferative phase involves fibroblast activity with the production of collagen, angiogenesis, and re-epithelialization of the wound surface. The remodeling phase is characterized by the maturation of collagen with the realignment

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of its fibers along the lines of the lesion and wound contraction.

The wound healing process is a simple yet intricate process in which various growth factors cause cell proliferation, thus causing integration of dynamic changes that involve soluble mediators, blood cells, parenchymal cell proliferation, and production of the extracellular matrix.[2]

Multiple factors influence wound healing and can interfere with one or more phases leading to delayed or impaired wound healing.[3] An appropriate oxygen level is crucial for optimum wound healing. Infections, desiccation, maceration, necrosis, systemic steroids, and chronic diseases delay wound healing. Wound healing delays as age advances.

pH plays a very important role in wound healing. pH of the wound is an indicator of biochemical processes of healing and hence can be monitored to look at healing progression.[4] Acidic pH helps in wound healing by controlling infections, increasing antimicrobial activity, altering protease activity, reducing bacterial toxicity, and promoting epithelization and angiogenesis.

Aims and objectives

This study aimed to compare the effectiveness of citric acid versus superoxide ions in wound healing.

Materials and Methods

A randomized, prospective comparative study was conducted in a total of 100 patients admitted at Guru Nanak Dev Hospital, attached to Government Medical College, Amritsar. The study was conducted in a total of 100 patients. Cases having wounds with infection of any type (acute abscesses, chronic leg ulcers, Fournier's gangrene, burns, traumatic wounds, postsurgical wounds, pressure sores, bedsores, fasciitis, sinuses, and fistulas) were taken up for the study. The above cases were divided as 50 each into two Groups – A and B.

Group A

The skin around the wound site was painted with povidone-iodine. The wound was then cleaned with normal saline, and superoxide ions solution will be applied. Dressing was done by using paraffin gauze.

Group B

The skin around the wound site was painted with povidone-iodine. The wound was then cleaned with normal saline. The dressing was done using autoclaved gauze. In addition, the 3% citric acid solution was applied.

Inclusion criteria

For this study, patients having wounds (acute abscesses, chronic leg ulcers, gangrenous wounds, Fournier's gangrene, burns, traumatic wounds, postsurgical wounds, pressure sores, bedsores, fasciitis, sinuses, fistulas, and carbuncles) were taken up for study.

Exclusion criteria

Patients having:

1. Fever
2. Altered consciousness
3. Pre diagnosed cases of diabetes mellitus
4. Diagnosed cases of systemic diseases such as tuberculosis, leprosy, etc.
5. Hypoproteinemia
6. Signs of septicemia
7. Vascular diseases.

The patients were divided into two groups: Group A where wound management was done using superoxide ions and Group B where citric acid was used. An attempt was made to include similar types of cases in both the study groups. Informed consent was obtained in all the cases, and demographic characteristics such as age and sex were noted. Other variables such as decrease in wound size, formation of granulation tissue, decrease in wound discharge, and pH values were compared in two groups.

Various investigations such as hemogram, blood sugar, urea, serum creatinine, serum proteins, electrolytes, and liver function tests wherever indicated were carried out.

Statistical analysis

All data were analyzed using SPSS IBM software (SPSS Inc., IBM). The values were expressed as mean ± standard deviation, percentages, and P values. The Student's t-test was used to compare the means, and the Chi-square test was used to compare the data; $P < 0.05$ was considered statistically significant.

Results

Wound size

In our study, the mean wound size before the treatment in Group A and B was 24.70 ± 24.86 and 25.50 ± 25.06, respectively. About 70% of the patients had wound size <40 cm^2 in both the groups (P = 1.000). Four patients with superficial burns (25%–50%) were also included in both the groups. Patients treated with citric acid showed an average reduction of wound size by 73.43% in 14 days as compared to 66.52% in the control group. The topical use of citric acid significantly (P = 0.032) increased the average reduction of wound size [Table 1].

Granulation tissue

The average increase in the percentage of granulation area in our study was more when citric acid was used for dressing (56.66%) than that in the control

group (50.87%). The difference seen in both the groups was statistically significant ($P = 0.050$) by the 12th day. On average, by the 12th day, more than 50% of the wound area showed granulation tissue when citric acid was used for topical dressing [Table 2].

pH

We assessed the pH of the wound surface on the 3rd, 7th, and 12th days using pH strips. The range of pH of the wound surface in most of the patients in the citric acid group was 4–6, while that in the control group was 6–8 [Tables 3-5].

Wound discharge

The wounds where citric acid was used for dressing showed an early reduction in the amount of discharge as compared to the superoxide ions group which was statistically evident by the 5th day. However, by the 12th day, most of the patients had scanty to minimal amount of discharge in both the groups [Tables 6-10].

Pain and hospital stay

In our study, the mean visual analog scale (VAS) score decreased from 6.50 on day 1 to 1.52 on day 14th in the control group. On the other hand, in the citric acid group, it decreased from 6.42 to 1.38 on respective days. There was no statistically significant difference in the VAS score for pain in both the groups. No systemic or local allergic manifestations were seen in the study except mild irritation and pain during the application of superoxide ions, especially in some hypersensitive patients.

The mean hospital stay in the patients of the citric acid group (8.36 days ± 4.42) was comparatively less than that of patients in the control group (10.92 days ± 7.44). In the control group, there were 10 patients who stayed in the hospital for more than 20 days. However, in the study group, only 1 patient stayed for 20 days.

Table 1: Distribution of patients according to the wound size (cm²) in Group A and B

Wound size (cm²)	Number of cases (%)	
	Group A	Group B
≤20	25 (50)	25 (50)
21-40	9 (18)	9 (18)
41-60	8 (16)	6 (12)
61-80	3 (6)	2 (4)
>80	1 (2)	4 (8)
Burn 25%	1 (2)	1 (2)
Burn 30%	1 (2)	1 (2)
Burn 40%	1 (2)	1 (2)
Burn 50%	1 (2)	1 (2)
Total	50 (1000)	50 (100)
Mean±SD	24.70±24.86	25.50±25.06
P	0.873	

Unpaired *t*-test. SD: Standard deviation

Table 2: Comparison of average (percentage) increase in granulation area (cm²) on different days

	Mean±SD		*t*	*P*
	Group A	Group B		
Day 5	20.70±7.69	23.80±9.08	−1.837	0.070
Day 9	39.66±11.11	43.88±14.98	−1.592	0.113
Day 12	50.87±12.19	56.66±16.63	−1.982	0.050
Day 14	59.57±13.34	65.36±15.79	−1.980	0.051

Unpaired *t*-test. SD: Standard deviation

Table 3: Number of patients according to the average pH of the wound on day 3 in Groups A and B

pH	Group A, *n* (%)	Group B, *n* (%)
2-4	-	-
4-6	-	41 (82)
6-7	18 (36)	7 (14)
7-8	32 (64)	2 (4)
Total	50 (100)	50 (100)

Table 4: Number of patients according to the average pH of the wound on day 7 in Groups A and B

pH	Group A, *n* (%)	Group B, *n* (%)
2-4	-	4 (8)
4-6	-	41 (82)
6-7	25 (50)	5 (10)
7-8	25 (50)	-
Total	50 (100)	50 (100)

Table 5: Number of patients according to the average pH of the wound on day 12 in Groups A and B

pH	Group A, *n* (%)	Group B, *n* (%)
2-4	-	-
4-6	-	50 (100.0)
6-7	12 (24)	-
7-8	38 (76)	-
Total	50 (100)	50 (100)

Table 6: Number of patients according to the amount of discharge of the wound on day 1 in Groups A and B

Amount of discharge	Group A, *n* (%)	Group B, *n* (%)
None	12 (24)	11 (22)
Scanty	4 (8)	5 (10)
Minimal	8 (16)	11 (22)
Moderate	12 (24)	11 (22)
Copious	14 (28)	12 (24)
Total	50 (100)	50 (100)
χ^2	0.826	
Degree of freedom	4	
P	0.935	

Chi-square test

Discussion

In the current study, the effect of superoxide ions versus citric acid on wound healing was studied, and it was found that citric acid-treated wounds showed better results without any pain and allergic manifestation.

The wounds treated with citric acid showed an average reduction in wound size of 73.43% by the 14th day as compared to 66.52% in the control group. The difference seen in the average reduction of wound size was statistically significant (P = 0.032). This shows that the wounds treated with citric acid show more reduction in wound size as compared to those treated by superoxide ions.

Similarly, 50 of 52 cases of snakebite ulcers (at MIMSR Medical College, Latur) showed complete healing in 16–43 applications of 3% citric acid. All these cases were resistant to common antibiotics.[5] In another study, Prabhu *et al*. used 3% citric acid for topical application in 25 patients and a remarkable reduction in wound size (82.01%) was noted.[6]

The significant difference was seen in the percentage increase in granulation tissue in wounds treated in both the groups by the 12th day (P = 0.050). The wounds treated by citric acid application showed an average increase in granulation tissue of 56.66% as compared to 50.87% in the wounds treated by superoxide ions. This shows that the application of citric acid promotes the formation of granulation tissue.

Nagoba *et al*. studied the histopathological response of chronically infected wounds following citric acid application and showed that citric acid boosts fibroblast growth and neovascularization.[7] In another study, Nagoba *et al.* also found that 69 of 70 cases of surgical site infections showed the formation of healthy granulation tissue in 6–25 applications of 3% citric acid.[8]

The number of patients with moderate to copious discharge reduced significantly in patients treated with citric acid as compared to the control group by the 9th day (P = 0.004). This shows that citric acid has antimicrobial action.

Similarly, Nagoba *et al*. found *Pseudomonas aeruginosa* as the most common bacterial isolate on burn patients followed by *Staphylococcus aureus*. The application of citric acid to 46 burn patients resulted in complete healing in 40 (86.95%) cases in 7–25 applications. However, in the control group, conventional antibiotic therapy and local wound care resulted in complete healing in nine (45%) patients only.[9] *P. aeruginosa* was also found to be the most common isolate from surgical

Table 7: Number of patients according to the amount of discharge of the wound on day 1 in Groups A and B

Amount of discharge	Group A, *n* (%)	Group B, *n* (%)
None	12 (24)	11 (22)
Scanty	4 (8)	5 (10)
Minimal	8 (16)	11 (22)
Moderate	12 (24)	11 (22)
Copious	14 (28)	12 (24)
Total	50 (100)	50 (100)
χ^2	0.826	
Degree of freedom	4	
P	0.935	

Chi-square test

Table 8: Number of patients according to the amount of discharge of the wound on day 9 in Groups A and B

Amount of discharge	Group A, *n* (%)	Group B, *n* (%)
None	10 (20)	14 (28)
Scanty	8 (16)	9 (18)
Minimal	11 (22)	21 (42)
Moderate	11 (22)	6 (12)
Copious	10 (20)	0 (00)
Total	50 (100)	50 (100)
χ^2	15.3	
Degree of freedom	4	
P	0.004	

Chi-square test

Table 9: Number of patients according to the amount of discharge of the wound on day 12 in Groups A and B

Amount of discharge	Group A, *n* (%)	Group B, *n* (%)
None	6 (12)	12 (24)
Scanty	8 (16)	14 (28)
Minimal	20 (40)	21 (42)
Moderate	16 (32)	3 (6)
Copious	0 (0)	0 (0)
Total	50 (100)	50 (100)
χ^2	15.5	
Degree of freedom	4	
P	0.04	

Chi-square test

Table 10: Number of patients according to the amount of discharge of the wound on day 14 in Groups A and B

Amount of discharge	Group A, *n* (%)	Group B, *n* (%)
None	14 (28)	22 (44)
Scanty	8 (16)	14 (28)
Minimal	10 (20)	14 (28)
Moderate	12 (24)	0 (0)
Copious	6 (12)	0 (0)
Total	50 (100)	50 (100)
χ^2	22.1	
Degree of freedom	4	
P	0.001	

Chi-square test

site infections. All the isolates were inhibited by citric acid.[8]

There was no statistically significant difference in the VAS score for pain in both the groups. No systemic or local allergic manifestations were seen in the study except mild irritation and pain during the application of superoxide ions, especially in some hypersensitive patients.

The average pH of the wound surface in patients treated with citric acid was 4–6 as compared to 6–8 in the control group.

Citric acid has been used to acidify the milieu of wound surface. Prabhu *et al*. found that the wound environment was acidic (4–6) when citric acid was used for topical dressings.[6]

The average hospital stay in patients of Group B was comparatively less than that of patients in Group A. One patient treated with citric acid stayed for more than 20 days. On the other hand, in the control group, there were 10 patients who stayed for more than 20 days in the hospital.

Conclusion

This present study was undertaken to evaluate the comparative effect of superoxide ions versus citric acid on the healing of different wound types. We took 100 patients for the study. The patients were divided into two groups: Group A where wound management was done using superoxide ions and Group B where citric acid was used. The attempt was made to include similar types of cases in both the study groups.

It was concluded that citric acid is safe and effective in all types of wound management and gives better efficacy, faster response, and shorter hospital stay as compared to superoxide ion dressing.

Treatment with citric acid reduces the microbial flora by reducing the pH and is less painful during cleaning and debridement procedures. It can be used safely in various conditions such as chronic foot ulcers, bedsores, burns, traumatic wounds, postoperative infective wounds, cellulitis, and abscesses.

The topical application of citric acid remarkably reduces common signs of inflammation such as edema, wound discharge, and erythema. The use of citric acid promotes wound healing by the formation of granulation tissue and fibroblast proliferation. Global efficacy evaluation also confirms the superiority of citric acid over other antiseptics as good to excellent – efficacy response was recorded in a relatively more number of patients in citric acid-treated group as compared to other antiseptics.

The result of this study, therefore, appears to show more favorable results for the citric acid group than for superoxide ions. However, although the results are statistically significant, the strength of evidence depends on the study design. The results of this study justify further research into the use of 3% citric acid in treatment of various wounds and ulcers. It is important to ensure that possible sources of bias in further studies are excluded, for example, by randomization of patients to treatment and by blinded assessment of outcomes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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