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Efficacy of Collagen Granule Dressing and Normal Saline Dressing in Chronic Nonhealing Wounds in Lower Limbs - A Single Blinded Randomized Controlled Trail in a Tertiary Care Hospital in Chengalpattu District

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Abstract: ***Background***: Collagen, a fibrous and proline-rich protein made up of three α-chains, plays a crucial role in every stage of wound healing. It attracts fibroblasts and keratinocytes, promoting, angiogenesis, and re-epithelialization ***Methods***: This is a Single-blinded - Randomized control trial study was carried out in the Department of General Surgery at KarpagaVinayaga Institute of Medical Sciences and Research Centre in Chengalpattu district, involving patients withchronic non healing lower limb wounds from December 2023 to March 2024. The study included 60 patients diagnosed with chronic foot ulcers. The simple random sampling method was used. The patients were allocated based on the random number-generating process method and divided into two groups. Group A considered as collagen (trial group) and Group B is the control group (Normal Saline). ***Results*:** Among the both groups collagen dressing group took 25 Days to heal the wound and normal saline group took more than 30 days to heal the wound and growth of granulation tissue was 80% with in the 1st week and it took 2 weeks for normal saline group**.** ***Conclusions***: Collagen dressings enhance wound healing in diabetic foot ulcer patients, reducing both hospital stays and the need for split-thickness skin grafts/Flap cover. Our study concludes that collagen dressings are more effective than conventional dressings.
Keywords: Diabetic foot ulcer, Collagen, Normal salineand Chronic Ulcer**.**

INTRODUCTION

The prevalence of Chronic non-healing wounds is quite increasing among US Medicare beneficiaries from 2.3 million (2014) to 10.5 million (2019) which will be a burden to the people.

An ulcer is defined as a break in the continuity of the covering epithelium, whether it be skin or mucous membrane. Chronic non-healing wounds are the leading cause of the rise in morbidity and mortality. Chronic non-healing wounds, which are characterized by the slow and non-healing break in the skin layers of the lower limb, persist

for over six weeks [1-3]. Growth factors and cytokines are insufficient in chronic non-healing wounds, which hindersthe healing process. These non-healing wounds not only affect health but also negatively affect nearly every aspect of daily life. They can lead to restricted mobility, sleep disturbances, decreased work capacity, and financial strain for the affected individuals. As such, their effects are detrimental to the patient's productivity as well as their quality of life. Among them, Diabetic foot ulcers are more common.

Diabetic foot ulcers are a severe and frequent consequence of diabetes mellitus, greatly increasing treatment expenditures. According to the Centers for Disease Control and Prevention's National Diabetes Statistics Report, 38.4 million people in the United States have diabetes, accounting for 11.6% of the population [4]. Diabetic foot ulcers are the major cause of lower leg amputations in diabetic patients, requiring surgery in 85% of amputation cases due to ulcer development [6, 7]. An important concept is that wound healing follows defined stages.With an understanding of the processes of wound healing, one can manipulate healing to reach the best results in a short period [9, 10]. Wound management has become a societal burden, and it is increasing by the day. Delayed wound healing increases the mental, physical, and financial stress on both the individual and the healthcare system. Among them, diabetic foot ulcers contribute a significant amount [11].

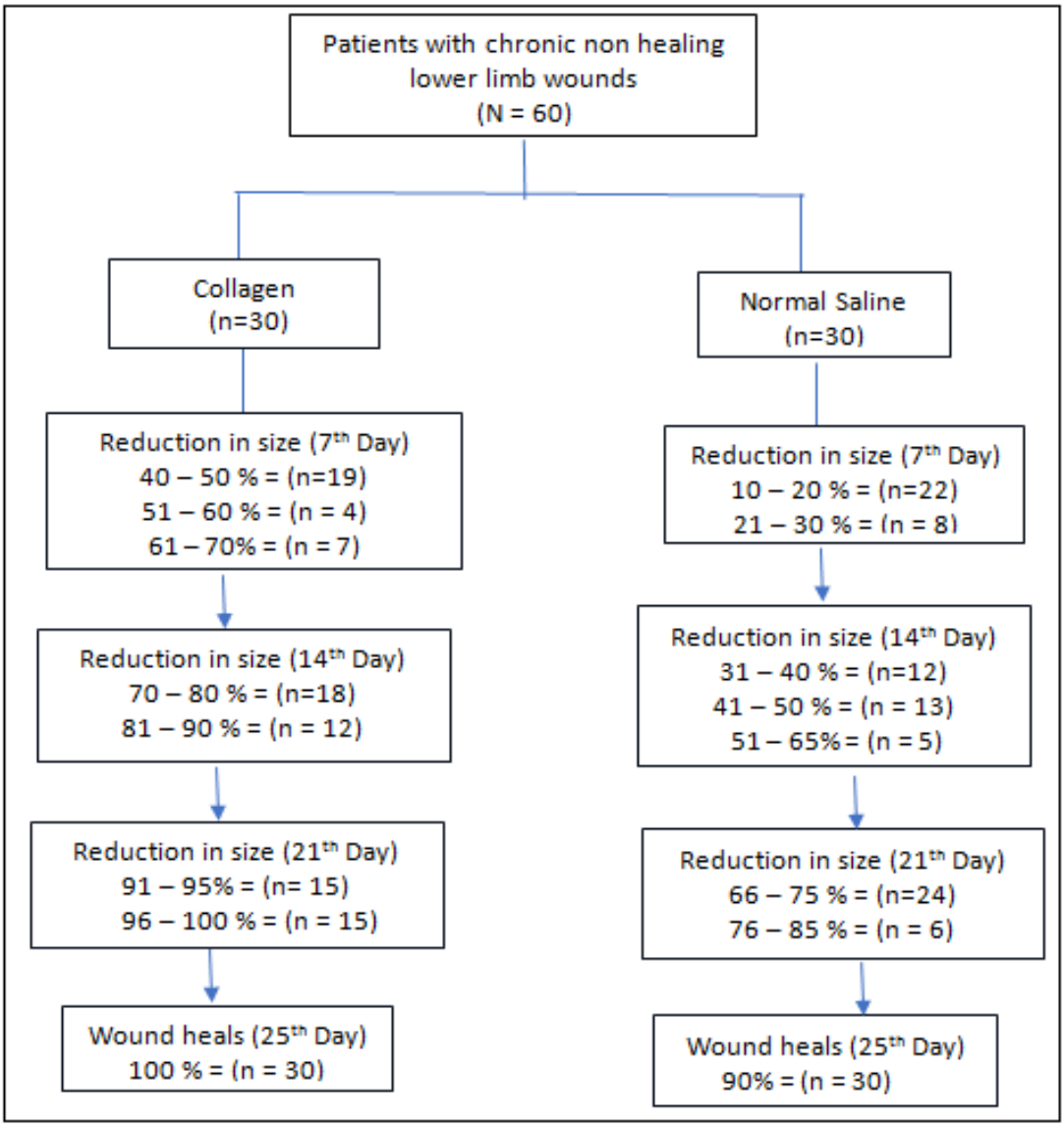
In the past decade, various new dressing materials have been developed, including calcium alginate, hydrocolloid membranes, and fine mesh gauze. However, these materials have the disadvantage of becoming permeable to bacteria [5]. As a key component of the extracellular matrix, collagen is vital for the human body, influencing the tensile strength of connective tissues and providing muscle strength and flexibility. Collagen is a fibrous protein found in skin, bones, tendons, cartilage, blood vessels, and teeth, and is commonly used as a medical device due to its simple form and manageability.

In modern medical settings, various dressing materials such as collagen fibers, membranes, gels, and sponges are employed. Due to its hemostatic effect and minimal antigenicity, collagen implants have been shown in animal experiments to have survival rates ranging from 80% to 100%. The materials also exhibit stability for several weeks following surgery without inducing foreign body reactions or inflammatory reactions. Because of its well-preserved main sequence and helix structure, it has a low rate of immunological rejection in humans [12, 13]. Promising outcomes have been obtained from the successful application of collagen in biocompatible dressing materials for various wounds, including burns and ulcers [8].

Materials and Methods

This is a Single-blinded - Randomized control trial study carried out in the Department of General Surgery at KarpagaVinayaga Institute of Medical Sciences and Research Centre in Chengalpattu district, involving diabetic foot ulcer patients from December 2023 to March 2024. The study included sixty members diagnosed with chronic non-healing wounds. The simple random sampling method was used. The patients were allocated based on the random number-generating process method and divided into two groups. Group A considered as collagen (trial group) and Group B is the control group (Normal Saline). This study evaluates the effectiveness of collagen dressings compared to commonly used dressings like normal saline in treating chronic nonhealing wounds in lower limbs. In both groups, observations and analyses were conducted regarding age, gender, duration of hospital admissions, reduction in ulcer size throughout follow-up, and percentage of granulation growth. Swabs from wounds were taken upon admission and again as needed. Before applying a bandage, the affected area will be cleaned and debrided if necessary. Based on the sensitivity of their wound cultures, both groups were treated with antibiotics.

Flow Chart for Random Allocation



Inclusion Criteria

Ulcers of duration more than weeks, patients willing to study, and wounds of size 6 and greater than 6 cm after taking consent were included in the study.

Exclusion Criteria

The patients with malignant ulcers, osteomyelitis, malnutrition, patients on immune-suppressants and were excluded from the study.

Sample Size Calculation

Ital Rajesh K. Jegoda (2020) reported the Mean ulcer size at day 1 in group A (collagen granules) was 16.29 cm^2 with an SD of 6.07 cm2. In Group B (normal saline), the mean ulcer size at day 1 was 14.73 cm^2 with an SD of 6.37 cm^2 in the most recent edition of the International Surgery Journal. Based on this as a reference and a 95 % confidence interval, the mean difference between the two groups will be 3 and the minimum sample size will be 33 ~ 40. Each group allocated 30 patients.

Consent: Signed informed consent was obtained after explaining the study method to the participants, and ethical committee approval was secured before patient recruitment. Patients provided written consent after being informed about the study's nature and purpose. They were guaranteed strict confidentiality and were always given the option to withdraw from the study.

Statistical Analysis

All the data were entered into a Microsoft Excel sheet and verified before analysis using SPSS 25.0. It shows that the observed data were not normally distributed.The experimental values were tabulated using frequency and percentage. Continuous variables like age and reduction in wound size were expressed as the mean and standard deviation. Categorical variables are age, gender, size of wound, and number of hospital studies applied to frequency and percentage. In inferential statistics, dichotomous data or ordinal data were applied to the $\chi 2$test, and continuous types of data were done for students't-tests for the reduction of wound size on the 7th, 14th, 21st, 25th, and 30th days. This p-value< 0.05 is significant at the 5% level of confidence interval.

RESULT

Table 1: Descriptive statistic for study parameters

Study Parameter	Frequency (n = 60)	%
Age		
< 50	21	35.0
50 – 60	34	56.7
> 60	5	8.3
Gender		
Female	27	45.0
Male	33	55.0
Smoking		
Absent	35	58.3
Present	25	41.7
Alcohol		
Absent	31	51.7
Present	29	48.3
Antibiotics given in days		
< 6	25	41.7
6 - 9	6	10.0
> 9	29	48.3
Hospital stays in days		
< 24	17	28.3
24 – 28	22	36.7
> 28	21	35.0

From Table 1, Most of the patients are in the age group of 50–60 (56.7%) years, making up more than half of the study population. Only a small proportion are older than 60 (8.3%). The patients are relatively balanced in terms of gender, with a slight majority being male. A larger portion of the sample does not smoke, with nearly 60% being non-smokers. The distribution of alcohol consumption by the patient is comparatively high; the consumed alcohol is 51.7%. The majority of individuals who received antibiotics for more than 9 days were 48.3%. A smaller group received antibiotics for less than 6 days (41.7%), and an even smaller group for 6–9 days (10.0%). Hospital stay durations are fairly spread out across the categories, with the largest group staying for 24-28 days. The next largest group stayed for more than 28 days, and the smallest group stayed for less than 24 days. More participants are non-smokers and have a nearly equal distribution regarding alcohol consumption.

Table 2: The association between outcome parameters for Collagen versus Normal Saline groups

Outcome Parameters	Collagen (n = 30) %	Normal Saline (n = 30) %	P Value
Hospital Stay in days			
< 24	17 (100.0)	0 (0.0)	0.000**
24 – 28	13 (52.0)	12 (48.0)	
> 28	0 (0.0)	18 (100.0)	
No of days of Antibiotic			
< 6	25 (100.0)	0 (0.0)	0.000**
6 to 9	5 (83.3)	1 (16.7)	
> 9	0 (0)	29 (100)	
Size of ulcer in admission time			
< 9	21 (70.0)	29 (96.7)	0.020*

9 to 12	6 (20.0)	1 (3.3)	
> 12	3 (10.0)	0 (0.0)	
Alcohol			
Absent	15 (48.4)	16 (51.6)	0.796
Present	15 (51.7)	14 (48.3)	
Smoking			
Absent	14 (40.0)	21 (60.0)	0.067
Present	16 (64.0)	9 (36.0)	

****** Highly significant at 5% level. * Significant, χ^2 test

Based on the data presented in Table 2, it was observed that all patients in the collagen group had significantly shorter hospital stays (less than 24 days) compared to the normal saline group. The collagen group also required fewer days of antibiotic treatment (less than 6 days for all patients) in comparison to the normal saline group. Additionally, a significantly higher proportion of patients in the collagen group had smaller ulcers (less than 9) as compared to the normal saline group. There was no significant difference in alcohol consumption between the two groups; however, it is worth noting that a higher proportion of smokers were observed in the collagen group (64%) compared to the normal saline group (36%). These findings suggest that collagen treatment may be linked to shorter hospital stays, reduced antibiotic use, and potentially smaller ulcers upon admission when compared to normal saline.

Table 3: Reduction of wound size per 100 percentage

Wound Size	**Collagen (n = 30)**	**Normal Saline (n = 30)**	**P Value**
	Mean ± SD	**Mean ± SD**	
7th day	52.1 ± 10.0	18.8 ± 6.5	0.000
14th day	80.6 ± 6.2	45.1 ± 7.9	0.000
21th day	96.1 ± 4.2	73.5 ± 5.8	0.000
25th day	100 ± 0.0	89.1 ± 6.0	0.000
30th day	0.0 ± 0.0	93.3 ± 25.3	0.000

****** Highly significant at 5% level, P < 0.05

The table 3 provides the mean and standard deviation (SD) of wound size reduction in percentages for participants treated with collagen and normal saline over different periods. The P values indicate the statistical significance of the differences between the two groups. The results show that wound size reduction is significantly greater in the collagen group compared to the normal saline group on the 7th, 14th, and 21st days. By the 25th day, the collagen group achieves complete wound size reduction (100%), which is significantly higher than the normal saline group. However, there appears to be an anomaly on the 30th day, as the collagen group shows a 0.0% reduction, despite having achieved a 100% reduction by the 25th day. Normally, once a wound is fully healed, the wound size reduction should remain at 100%. The normal saline group, on the other hand, shows a significant but less complete reduction. Across all time intervals, the P values indicate highly significant differences in wound size reduction favoring collagen over normal saline. The following are figures – Fig 1 At the time of admission, Fig 2 After wound debridement, Fig 3 At day 14, Fig 4 At day 21 for which collagen granules were used

Table 4: Granulation tissue growth per100 percentage

Granulation tissue	**Collagen (n = 30)**	**Normal Saline (n = 30)**	**P Value**
	Mean ± SD	**Mean ± SD**	
7th day	74.3 ± 5.9	26.5 ± 7.7	0.000
10th day	100 ± 0.0	63.1 ± 14.8	0.000
14th day	100 ± 0.0	100 ± 0.0	0.000

From Table 4, the average granulation tissue growth was 74.3% ± 5.9% for collagen and 26.5% ± 7.7% for normal saline. Granulation tissue growth was significantly different between the treatment group and control group by the 7th day. By the 10th day, the collagen group achieved complete granulation tissue growth (100%), which was significantly higher than the normal saline group. On the 14th day, both groups achieved complete granulation tissue growth (100%). However, the P value suggests a significant difference, which could be an anomaly or error since both means are 100%. The P values across all time intervals indicate highly significant differences in granulation tissue growth favoring collagen over normal saline, except for the 14th day when both groups achieved 100%. Overall, the collagen treatment leads to significantly faster and more complete granulation tissue growth compared to normal saline, particularly noticeable by the 7th and 10th days.

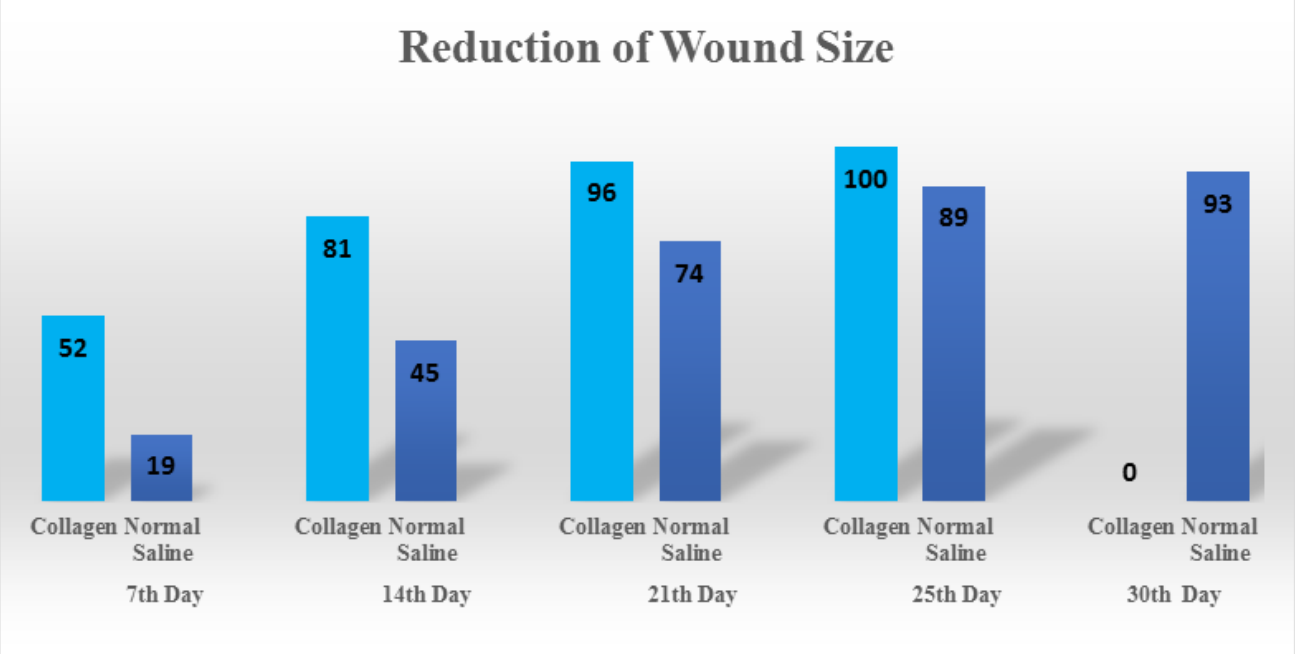


Chart 1: Bar chart for Reduction of Wound Size

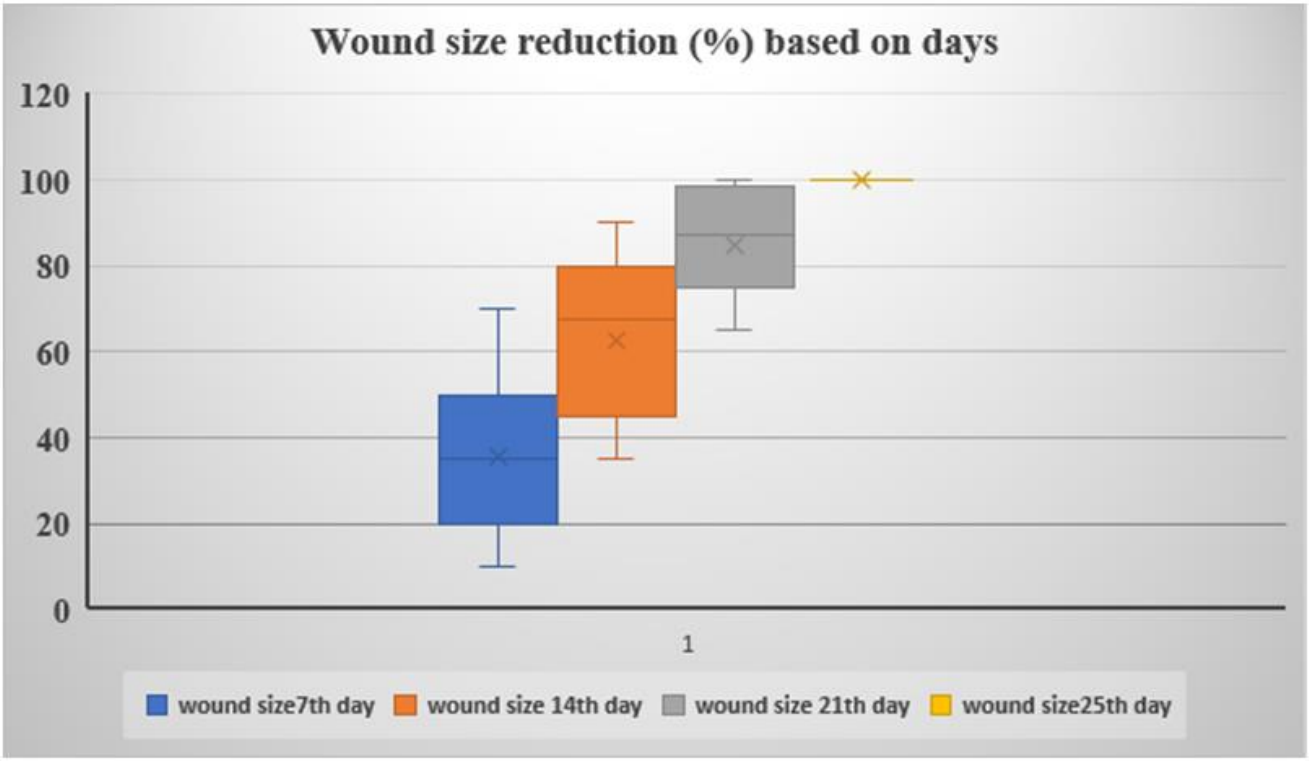


Chart 2: Box Plot for Wound Size reduction (%) based on days

At the time of admission after debridement

Figure 1:

Figure 2:

At 14th day of collagen dressing At 21st day of collagen dressing

Figure 3:

Figure 4:

DISCUSSION

In this study,the Collagen group gave better results when compared to the normal saline group regarding decreasing the wound size in percentage at days 7, 14, 21, and 25 are 52%, 80%, 96%, and 100% respectively and the saline group with a reduction in size at day 7, 14, 21, 25, 30 are 18%, 45%, 89%, and 93% respectively. The growth of granulation tissue was 80% on the 7th day and 100% on the 10th day in the collagen group and in the normal saline group 26%, 63%, and 100% on the 7th, 10th and 14th day respectively. The number of hospital stay days was lesser in the collagen group < 24 days was 17 members and 24 to 28 days were 13 members whereas in the saline group no patient was discharged < 24 days, between 24 to 28 days were 12 members and 18 members stayed > 28 days. The use of antibiotics was less in the collagen group when compared to the normal saline group.

In a case study by MohamadAsadJuneja on diabetic foot treatment, it was observed that the emergence of healthy granulation tissue occurred significantly faster in patients treated with medicated collagen powder dressings (9 days) compared to those with conventional dressings (15 days). Additionally, the duration of antibiotic treatment was notably shorter for patients using medicated collagen powder dressings (5 days) versus those with conventional dressings (8 days). The study also revealed that the total hospital stay was significantly reduced for patients treated with medicated collagen powder dressings (13 days) compared to those receiving conventional dressings (21 days).

Omkar Singh's study involving 120 patients with chronic wounds of various causes, with an average age of 43.7 years, revealed that after two weeks of treatment, 60% of wounds in the 'collagen group' and only 42% in the 'conventional group' were sterile (P=0.03). Healthy granulation tissue developed earlier in wounds treated with collagen dressings compared to those treated conventionally (P=0.03). After eight weeks, 52 wounds (87%) in the 'collagen group' and 48 wounds (80%) in the 'conventional group' showed more than 75% healing (P=0.21). Therefore, we conclude that collagen dressings are more efficient than conventional Normal Saline dressing.

CONCLUSION

This data provides a demographic and clinical profile of the study participants, indicating the prevalence of certain characteristics and treatments within the sample. These results suggest that Collagen treatment may be associated with shorter hospital stays, reduced antibiotic use, and potentially smaller ulcers at admission compared to Normal Saline. This appears to be an anomaly or error as the Collagen group shows a 0.0% reduction at 30 days despite having achieved a 100% reduction by the 25th day. Typically, once a wound is fully healed, the wound size reduction remains at 100%. The Normal Saline group, on the other hand, continues to show a significant but less complete reduction. Demonstrates significantly faster granulation tissue growth at each measured interval compared to the Normal Saline group. Shows slower and less complete granulation tissue growth by the 7th and 10th days but catches up by the 14th day.

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