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Efficacy of concentrated growth factors (CGF) vs normal saline dressing in chronic non healing ulcers

Chanjiv Singh^{1,*}, Amit Kumar², Gursehaj Singh Mehta³¹Dept. of Plastic Surgery, Armaan Hospital, Jalandhar, Punjab, India²Dept. of General Surgery, Civil Hospital, Jalandhar, Punjab, India³Dept. of General Surgery, Institute for Supply Management, Bishkek, Kyrgyzstan

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ABSTRACT

A Chronic non-healing wound is one which fails to progress through a timely sequence of repair or one that proceeds through the wound healing process without restoring anatomic and functional results. A wide variety of factors is thought to contribute to this problem. Concentrated Growth Factors (CGF) (first developed by Sacco (2006)) is a relatively new technology within the area of regenerative medicine. CGF is an advanced second generation platelet concentrate, obtained with differential continuous centrifugal technology. Use of CGF in management of chronic skin wounds has led to high rates of recovery but further works are required in order to improve the effectiveness of treatment protocols and the comfort and safety of patients. Its application is progressively spreading in the clinical field.

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1. Introduction

Patients with chronic wounds constitute a significant workload burden for health care organizations. Patients with chronic wounds may experience prolonged hospitalization, increased financial burden, chronic pain, increased morbidity and mortality.^{1,2}

A Chronic non-healing wound is one which fails to progress through a timely sequence of repair or one that proceeds through the wound healing process without restoring anatomic and functional results. Although there is no clear consensus in the duration of a wound that defines chronicity, a range of 4 weeks to 3 months has been used to define chronic wounds in the literature. A wide variety of factors is thought to contribute to this problem, affecting all phases of wound healing and seemingly nearly every molecule involved in this process.^{3,4}

CGF first developed by Sacco (2006) is a relatively new technology within the area of regenerative medicine. CGF is an advanced second generation platelet concentrate, obtained with differential continuous centrifugal technology, containing many kinds of growth factors and fibrins, and able to facilitate the recovery of soft and hard tissues. CGF is different from platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in the methods for production. CGF has a higher adhesive strength, tensile strength, higher viscosity than the other platelet preparations. CGF is a fibrin rich organic matrix which contains growth factors, platelets, leukocytes and CD34+ stem cells which help in the process of regeneration and also has immunological cells that are effective in regulating inflammation and minimizing the risk of infection.⁵

Use of CGF in management of chronic skin wounds has led to high rates of recovery^{6,7} but further works are required in order to improve the effectiveness of treatment protocols and the comfort and safety of patients. Its

* Corresponding author.

E-mail address: chanjivmehta@gmail.com (C. Singh).

application is progressively spreading in the clinical field. Relatively few studies have been published on this topic, hence the literature on this needs more validation before its widespread use.

2. Aim and Objectives

To compare the effectiveness of concentrated growth factors (CGF) in comparison to normal saline dressing in the healing of chronic ulcers in a blind study.

3. Material and Methods

This study was undertaken in the Department of Surgery, SBLS Civil Hospital Jalandhar, Punjab as a randomized, prospective, parallel group study from Dec 2019 - June 2021. All the patients with chronic wound ulcers from age group 18-60 years were included in the study. Informed consent for the study was obtained. A total of 100 patients with chronic wound ulcers were randomly divided into one of the following two groups (50 each) using computer generated random numbers. The study group was treated with local application of concentrated growth factor (CGF) along with the required wound care and the Control group was subjected to standard wound Care with normal saline dressing. Patients excluded from the study were Patients with osteomyelitis, with grossly impaired RFT/LFT, known cases of malignancy, diabetes, severe cardiovascular issues, bleeding disorders, pregnant women and Patient on corticosteroid/immunosuppressive and chemotherapeutic drugs.

3.1. Preparation of CGF

Venous blood was centrifuged in special machine (Medifuge CGF MF200 Silfradent S.R.L. Sofia, FC, Italy) which yielded three blood fractions (see diagram no). The CGF gel layer was separated and transferred into a petri dish. The CGF gel was compressed to create a sheet of CGF membrane.

3.2. Treatment procedure

Initial debridement was done in case of unhealthy wounds followed by periodic debridement if required. Prophylactic antibiotic was prescribed during treatment. CGF membranes were applied over ulcers and covered with an occlusive dressing and changed in every 2-3 day in study group patients. Patients in control group had saline gauze dressings over target ulcer area and changed in every 2-3 days over a period of 8 weeks. Wound healing evaluation was performed at every fortnight visit. Information was collected by clinical examination and laboratory investigations.

3.3. Stastical analysis

All the data was noted down in a pre-designed study proforma. Qualitative data was represented in the form of frequency and percentage. Association between qualitative variables was assessed by Chi-Square test and Fisher's exact test for all 2×2 tables. Quantitative data was represented using Mean \pm SD. Analysis of Quantitative data between the two groups was done using unpaired t-test if data passed 'Normality test' and by Mann-Whitney Test if data failed 'Normality test'. A p value <0.05 was taken as level of significance. Results were graphically represented where deemed necessary. SPSS Version 21.0 was used for most analysis and Microsoft Excel 2010 for graphical representation.

4. Discussion

The history⁸ of wound healing is as old as the history of mankind. The earliest medical writings deal extensively with wound care. Seven of the 48 case reports included in the Edwin Smith Papyrus (1700 BC) describe wounds and their management. Empirically, the ancient physicians of Egypt, Greece Local factors affecting wound healing are Hypoxia and Infection while systemic factors are age, hormones, stress, Diabetes, medications including steroids and chemotherapeutic agents.

A chronic wound is a wound that does not heal in an orderly set of stages and in a predictable amount of time the way most wounds do; wounds that do not heal within three months are often considered chronic. Chronic wounds seem to be detained in one or more of the phases of wound healing. For example, chronic wounds often remain in the inflammatory stage for too long. In acute wounds, there is a precise balance between production and degradation of molecules such as collagen; in chronic wounds this balance is lost and degradation plays too large a role.⁹

Chronic wounds may never heal or may take years to do so. These wounds cause patients severe emotional and physical stress as well as creating a significant financial burden on patients and the whole healthcare system.

Chronic wounds mostly affect people over the age of 60. The incidence is 0.78% of the population and the prevalence ranges from 0.18 to 0.32%. As the population ages, the number of chronic wounds is expected to rise.⁹ Patients with Chronic wound often report pain as dominant in their lives.¹⁰

Persistent pain (at night, at rest, and with activity) is the main problem for patients with chronic ulcers. Frustrations regarding ineffective analgesics and plans of care that they were unable to adhere to were also identified. The Wound Healing Society classifies chronic wounds into 4 major categories: pressure ulcers, diabetic foot ulcers, venous ulcers, and arterial insufficiency ulcers. A small number of wounds that do not fall into these categories

may be due to causes such as trauma, immunosuppression, radiation poisoning, etc. In addition to poor circulation, neuropathy, and difficulty moving, factors that contribute¹ to chronic wounds include systemic illnesses, age and repeated trauma. Comorbid ailments that may contribute to the formation of chronic wounds include vasculitis (an inflammation of blood vessels), immune suppression, pyoderma gangrenosum, and diseases that cause ischemia. Immune suppression can be caused by illnesses or medical drugs used over a long period, for example steroids. Emotional stress can also negatively affect the healing of a wound, possibly by raising blood pressure and levels of cortisol, which lowers immunity. Repeated physical trauma plays a role in chronic wound formation by continually initiating the inflammatory cascade.

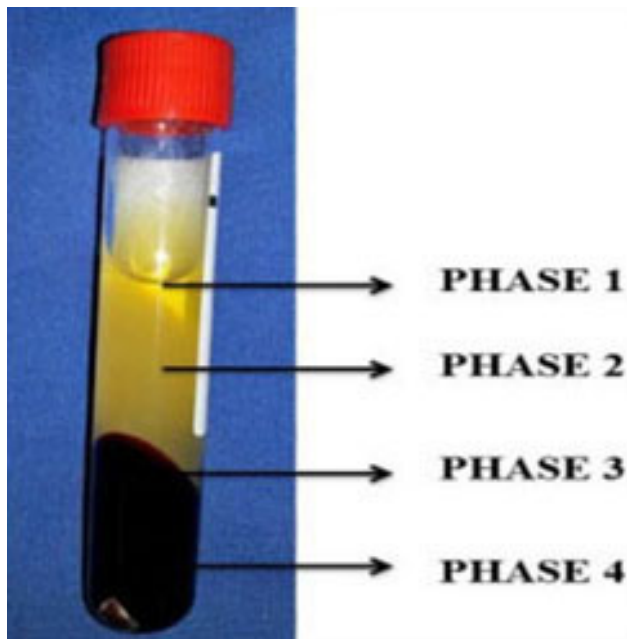


Fig. 1:

Phases of Centrifuged Blood

1. Superior phase – Serum
2. Interim phase – Fibrin buffy coat
3. Liquid phase – Growth factors
4. Lower phase — Red blood cells

Though all wounds require a certain level of elastase and proteases for proper healing, too high a concentration is damaging. Leukocytes in the wound area release elastase, which increases inflammation, destroys tissue, proteoglycans, and collagen, and damages growth factors, fibronectin, and factors that inhibit proteases. The activity of elastase is increased by human serum albumin, which is the most abundant protein found in chronic wounds. However, chronic wounds with inadequate albumin are especially unlikely to heal, so regulating the wound's

levels of that protein may in the future prove helpful in healing chronic wounds. Excess matrix metalloproteinases, which are released by leukocytes, may also cause wounds to become chronic. MMPs break down ECM molecules, growth factors, and protease inhibitors, and thus increase degradation while reducing construction, throwing the delicate compromise between production and degradation out of balance.

The CGF glue which is rich in growth factors is taken from the test tubes with tweezers and the two phases were cut off with scissors where the center and bottom layers connected. When the CGF glue is separated out, a quantity of growth factors are located on the interface between the CGF glue layer and the erythrocyte layer. Therefore, a certain amount of erythrocytes has to be retained when doing the separation to ensure the content of the growth factors. The CGF glue is pressed in moulds, squeezing the liquid elements within it and obtaining the CGF membrane. The CGF glue and the CGF membrane are put into sterile normal saline for future use.¹¹

CGF is a fibrin tissue adhesive with haemostatic and tissue sealing properties. It promotes wound healing and accelerates osteogenesis. CGF improves the stability of the wound that is required for the attachment of a new connective tissue to the root surface. It promotes epithelial, endothelial and epidermal regeneration and decreases scarring. It has antimicrobial properties due to high concentration of leukocytes. Fibrin plays a role in promoting injury healing and providing a natural material for the fibrin network scaffold.¹² The regular and cross-linked fibrin scaffold in CGF is formed with thin and thick fibrillary elements. The highly cohesive fibrin scaffold may provide protection for CGF from plasmin degradation. It also protects growth factors from proteolysis. The fibrin scaffold acts as a temporal nesting matrix for platelets, leukocytes and CD34-positive cells. It retains and later releases a portion of growth factors, avoiding the burst effect and providing physiological cytokines. Growth factors that are delivered “on demand” may promote greater biological effects, reducing risks of tissue edema and inflammatory responses that are caused by high concentrations of growth factors.

Endogenous Growth Factors¹² The centrifugation process triggers constant collision and rupture of platelets. Numerous platelets are caught into the dense fibrin scaffold simultaneously. Growth factors mostly investigated in CGF include platelet-derived growth factor (PDGF), transforming growth factor- β 1 (TGF- β 1), basic fibroblast growth factor (b-FGF), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF) and bone morphogenetic proteins (BMPs). CGF gradually delivers growth factors as it degrades gradually at local sites. To extract and quantify growth factors of CGF, the freeze-thaw and lyophilizing

methods were used.

Masaki et al.¹³ found CGF and A-PRF contained similar quantities of growth factors, but they contained higher quantities of TGF- β , PDGF and VEGF than PRP. Qiao et al.^[65] found that CGF, PRF and PRP were similarly concentrated in the quantities of TGF β , PDGF, VEGF and IGF-1, but the b-FGF quantities of CGF and PRF were higher than that of PRP. Lei et al.^[66] reported that A-PRF had higher levels of VEGF and TGF- β than CGF because the looser fibrin network of A-PRF could promote the accumulation of platelets. Differences in the release kinetics of growth factors and the method of extracting growth factors or small samples may cause discrepancies in the literature. More comparative studies are needed to prove whether CGF is superior in composition and efficacy.

Release Kinetics of Growth Factors¹⁰ The release kinetics of growth factors in platelet concentrates will directly influence patterns of bioactivity. Due to different levels of α -granules and mRNA in activated platelets, every type of growth factor has its special release kinetics. PRP has been reported to have an entire release of growth factors within 1 h, working in the early phase of the regenerative and reconstructive process. However, this release kinetics has decided its failure in matching the complicated and long-term regenerative process. Some studies showed that PRF delivered growth factors continually for 7 to 10 days, whereas A-PRF showed a 14-day steady release. As the fibrin scaffold degrades, the platelet masses were gradually decomposed, and then, growth factors released slowly into the local microenvironment. The release kinetics of CGF were reported to undergo two phases. The instant release was attributed to a great number of platelet activation and simple diffusion. The second phase was decided by slow degradation of the fibrin scaffold.

Borsani et al.^[69] found that each type of growth factor in CGF had its specific kinetics over a period of 8 days. Qin et al.¹⁴ found that CGF slowly released TGF- β 1 for more than 13 days and peaked on the 7th day. Honda et al.^[72] reported that CGF released growth factors for more than 13 days and had a higher peak concentration. Wang et al.¹⁵ reported that CGF could have an accumulative growth factors release for 14 days and then decreased sharply. The discrepancies in release kinetics in the literature are possibly caused by differences in volumes of blood samples and observation time.

Prolonging release duration of growth factors may match the long-term process of regeneration and reconstruction. Yu et al.¹⁶ reported the combination of CGF with intrafibrillarly mineralized collagen had a continuous release of growth factors for 28 days and had two peak concentrations. Similar results could also be seen from the combination of CGF with chitosan-alginate composite hydrogels or beta tricalcium phosphate.¹⁷ These combinations constitute a continuous drug delivery system

and may match the long-term process of regeneration and reconstruction.

Functions of Growth Factors in CGF (Table 1) The rationale of platelet concentrates is related to in situ delivery of growth factors.¹⁸ Growth factors in CGF initiate signaling cascades and further cause multiple intracellular biochemical changes through binding to the corresponding receptors.¹⁹ T PDGF is a mitogenic and chemotactic factor for multiple cells including mesenchymal stem cells (MSCs), fibroblasts, smooth muscle cells, chondrocytes, osteoblasts and endothelial progenitor cells.²⁰ It may stimulate collagen biosynthesis and angiogenesis.²⁰ VEGF stimulates migration and proliferation of vascular endothelial cells, significantly functioning in VEGF-induced angiogenesis and vascular permeability.^{21,22} IGF-I stimulates the proliferation and differentiation of MSCs in chondrogenesis.²³ It even accelerates peripheral nerve regeneration²⁴ and stimulates angiogenesis.²⁴ TGF- β 1 stimulates proliferation of MSCs and epithelial cells.^{25,26} Besides, it induces migration of Schwann cells. EGF generally promotes proliferation and migration of epithelial cells²⁷ and fibroblasts and stimulates new granulation tissue formation. b-FGF is a basic singlechain protein mitogenetic and angiogenetic agent for multiple types of cells such as preosteoblasts and osteoblasts. Ko et al.²⁸ reported that some growth factors such as TGF β 1 had a weak mitogenic effect on smooth muscle cells, but they could enhance the mitogenicity of PDGF- BB, b-FGF and EGF, indicating synergistic effects to some extent. BMPs mainly influence regeneration of bone and cartilage directly and indirectly due to osteogenesis and osteoinductive nature.^{29,30} Besides, BMPs can stimulate differentiation of MSCs into various cell types including chondroblasts and osteoblasts.^{2,31} To conclude, CGF may play a comprehensive role through multiple signals.

ROLE OF CGF IN CHRONIC WOUND HEALING Amato B et al.³² aimed to evaluate the additional benefits of the CGF compared to the standard of dressing and its effects on the dynamics of the healing process. Autologous CGFs were obtained from 100 patients with chronic mixed ulcers (venous ulcers in patients with II stage claudication) of the lower limbs in a multicentric controlled randomized study. The results showed a significant advantage in the use of CGF in association with cleansing and selective compression in the healing time and stabilization of mixed ulcers of the lower extremities. These results support the CGF's clinical use for improving clinical outcomes in mixed ulcers of the legs.

Kao CH et al.³³ studied the use of concentrate growth factors gel or membrane in chronic wound healing among 18 cases. Noticeable granulation tissue and regenerated epidermal coverage were observed in 16 patients who received CGF treatment over various time courses, thereby demonstrating the significant therapeutic effects of CGF

Table 1: Main bioactive growth factors released by activated platelets in CGF

Platelet-derived growth factor (PDGF)	A mitogenic and chemotactic factor.	It acts on multiple cells, including mesenchymal stem cells, human dermal fibroblasts, smooth muscle cells, chondrocytes, osteoblasts and endothelial progenitor cells. It also induces collagen biosynthesis and angiogenesis.
Vascular endothelial growth factor (VEGF)	A key factor in promoting angiogenesis and vascular permeability.	It accelerates neo-vascularization in soft and hard tissue.
Insulin-like growth factor- 1 (IGF- 1)	Functioning in proliferation and migration, differentiation in multiple cells	It shows a potential in increasing viability of cartilage grafting, accelerating regeneration of peripheral nerve and new bone formation.
Transforming growth factor- β 1(TGF- β 1)	A mitogenic and chemotactic factor in most physiological process. It may enhance the mitogenicity of PDGF, b-FGF and EGF	It promotes proliferation of mesenchymal stem cells, epithelial cells and Schwann cell. It also induces extracellular matrix biosynthesis.
Epidermal growth factor (EGF)	Acting as a mitogenic and chemotactic factor	It promotes proliferation and migration of epithelial cells and fibroblasts, stimulating new granulation tissue formation
Basic fibroblast growth factor (b-FGF)	A basic single-chain protein as mitogenetic and angiogenetic agent for preosteoblasts and osteoblasts	It may show a potential in inducing new bone formation
Bone morphogenetic proteins (BMPs)	Acting as an independent osteogenesis and osteoinductive factor	It may induce new bone and cartilage formation directly and indirectly

Table 2: Mean age comparison among study groups

Age (years)	Group	Mean	SD	p-value
	Controls	52.80	12.10	0.78
	CGF	53.60	11.90	

Table 3: Distribution of subjects based on gender

Sex	Group		Total
	Controls	CGF	
Female	18	14	32
	36.0%	28.0%	32.0%
Male	32	36	68
	64.0%	72.0%	68.0%
Total	50	50	100
	100.0%	100.0%	100.0%

p-value - 0.521

Table 4: Distribution of subjects based on type of Ulcer

UT Classification	Group		Total
	Controls	CGF	
Diabetes Ulcer	38	35	73
	76.0%	70.0%	73.0%
Pressure Ulcer	5	4	9
	10.0%	8.0%	9.0%
Venous Ulcer	7	11	18
	14.0%	22.0%	18.0%
Total	50	50	100
	100.0%	100.0%	100.0%

p-value - 0.57

Table 5: Comparison of groups as per appearance of granulation tissue

Granulation Tissue appearance	Group		Total	p- value
	Controls	CGF		
Week 1	9	26	35	<0.05
	18.0%	52.0%	35.0%	
Week 4	32	48	80	<0.05
	64.0%	96.0%	80.0%	
Week 8	41	49	90	<0.05
	82.0%	98.0%	90.0%	

Table 6: Mean comparison of wound surface area at each follow up

Wound Surface Area (cm sq)	Group	Mean	SD	p-value
After Debridement	Controls	142.57	20.21	0.79
	CGF	141.92	18.12	
Week 1	Controls	116.54	20.21	0.33
	CGF	84.52	18.12	
Week 4	Controls	74.35	19.12	< 0.05
	CGF	51.72	16.83	
Week 8	Controls	42.21	17.94	< 0.05
	CGF	24.37	14.41	

Table 7: Mean comparison of hospital stay between the groups

Hospital Stay	Group	Mean	SD	p-value
	Controls	17.23	4.32	<0.05
	CGF	11.13	5.34	

Table 8: Comparison of wound closure technique between the groups

Wound Closure	Group		Total
	Controls	CGF	
Secondary Intention	6	44	80
	72.0%	88.0%	80.0%
STSG	14	6	20
	28.0%	12.0%	20.0%
Total	50	50	100
	100.0%	100.0%	100.0%

p-value <0.05

treatment in overall wound healing. The other two patients with stasis ulcers in their calves failed to respond to the treatment because of the comorbidity of iliac vein thrombosis. In addition, by culturing HaCaT keratinocytes using CGF membrane as the foundation, we observed that HaCaT cells attached to the CGF membrane migrated and proliferated to form an epithelium like structure. Comprehensively, the clinical results infer that CGF gel can expedite the regeneration of the soft tissue at the wound, whereas CGF membrane may facilitate its marginal re epithelialisation. The combination of the two can promote autologous regeneration of both deep and superficial wounds effectively and safely. The effect of CGF in chronic wound healing was still not explored that much and more studies are required to establish its role as an effective dressing for chronic wounds. Complications of diabetes

increase with age. Also diabetes is disease of mostly elderly. Similar findings of highest incidence being in age group of 45 to 64 years in the National health department survey (N.H.D.S) at USA. In another similar study by Lone AM et al. mean age in CGF group was 53.79 years and in Normal saline group was 54.57 years. Male Preponderance was observed in both groups (68.3% in Control and 70% in CGF group respectively).

Wound Healing: At the end of 4 weeks, 96% cases in CGF group had granulation tissue as compared to 64% cases in control group. By end of 8 weeks, the rate was 98% and 82% respectively. The difference was statistically significant (p<0.05). The wound contraction rate was significantly faster with CGF therapy. The difference in the rate of wound contraction was apparent since 1st week and by week 8, mean percentage of wound contraction was 90.9% in CGF

group as compared to 74.54% in control group patients. The difference was statistically significant ($p < 0.05$). Wound surface area decreased significantly faster in CGF group patients as compared to control group. The difference was statistically significant from week 4 ($p < 0.05$). Closure by secondary intention was achieved in 88% and 72% patients of CGF and control group while skin grafting was required in 12% cases of CGF group as compared to 28% cases in control group respectively. Kao CH et al.³³ studied the use of concentrate growth factors gel or membrane in chronic wound healing among 18 cases. Noticeable granulation tissue and regenerated epidermal coverage were observed in 16 patients who received CGF treatment over various time courses, thereby demonstrating the significant therapeutic effects of CGF treatment in overall wound healing.

Main bioactive growth factors released by activated platelets in CGF

5. Result

A total of 100 subjects with chronic wound ulcers were randomly divided into one of the following two groups (50 each) using computer generated random numbers: A. Study group (CGF): treated with local application of concentrated growth factor (CGF) along with the required wound care and; B. Control group: subjected to standard wound Care with normal saline dressing.

1. Mean age of study subjects was 52.8 and 53.6 years in controls and CGF group respectively. The difference was statistically non-significant ($p = 0.78$).
2. Male Preponderance was observed in both groups (64% in controls and 72% in CGF group respectively). The difference was statistically non-significant ($p = 0.521$).
3. Most common type of chronic ulcer observed in present study was diabetic ulcer (73%) followed by venous ulcers (18%) and pressure ulcers (9%). No difference was seen in the study groups on the basis of type of ulcer ($p = 0.57$).
4. At the end of 4 weeks, 96% cases in CGF group had granulation tissue as compared to 64% cases in control group. By end of 8 weeks, the rate was 98% and 82% respectively. The difference was statistically significant ($p < 0.05$).

The wound contraction rate was significantly faster with CGF therapy. The difference in the rate of wound contraction was apparent since 1st week and by week 8, mean percentage of wound contraction was 90.9% in CGF group as compared to 74.54% in control group patients. The difference was statistically significant ($p < 0.05$).

Wound surface area decreased significantly faster in CGF group patients as compared to control group. The difference was statistically significant at week 4 and week 8 ($p < 0.05$).

Mean hospital stay was significantly more in cases managed by normal saline dressing as compared to CGF (17.23 vs 11.13 days; $p < 0.05$).

Closure by secondary intention was achieved in 88% and 72% patients of CGF and control group while skin grafting was required in 12% cases of CGF group as compared to 28% cases in control group respectively.

6. Summary

Present hospital based comparative study aimed at comparing the effectiveness of concentrated growth factors (CGF) vs normal saline dressing in chronic non healing ulcers.

1. Mean age of study subjects was 52.8 and 53.6 years in controls and CGF group respectively. The difference was statistically non-significant ($p = 0.78$).
2. Male Preponderance was observed in both groups (64% in controls and 72% in CGF group respectively). The difference was statistically non-significant ($p = 0.521$).
3. Most common type of chronic ulcer observed in present study was diabetic ulcer (73%) followed by venous ulcers (18%) and pressure ulcers (9%). No difference was seen in the study groups on the basis of type of ulcer ($p = 0.57$).
4. At the end of 4 weeks, 96% cases in CGF group had granulation tissue as compared to 64% cases in control group. By end of 8 weeks, the rate was 98% and 82% respectively. The difference was statistically significant ($p < 0.05$).

The wound contraction rate was significantly faster with CGF therapy. The difference in the rate of wound contraction was apparent since 1st week and by week 8, mean percentage of wound contraction was 90.9% in CGF group as compared to 74.54% in control group patients. The difference was statistically significant ($p < 0.05$).

Wound surface area decreased significantly faster in CGF group patients as compared to control group. The difference was statistically significant from week 4 ($p < 0.05$).

Mean hospital stay was significantly more in cases managed by normal saline dressing as compared to CGF (17.23 vs 11.13 days; $p < 0.05$).

Closure by secondary intention was achieved in 88% and 72% patients of CGF and control group while skin grafting was required in 12% cases of CGF group as compared to 28% cases in control group respectively.

7. Conclusion

Present study concluded that local application of concentrated growth factor appears to be superior compared to normal saline dressings in the treatment of chronic wounds in terms of early appearance of granulation

tissue, rapid contraction and decrease in hospital stay. We thus recommend use of concentrated growth factor in chronic wound management as first line therapy. We also recommend further studies with larger sample size to validate our observations in each specific type of chronic wounds viz. venous, diabetic and pressure ulcers.

8. Source of Funding

None.

9. Conflict of Interest


The author declares that there is no conflict of interest.

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Author biography

Chanjiv Singh, Consultant  <https://orcid.org/0000-0001-91256420>

Amit Kumar, Post Graduate

Gursehaj Singh Mehta, Post Graduate  <https://orcid.org/0000-0002-2720-3719>

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