

# Study of efficacy of superoxidised solution and gel (microdacyn) in the treatment of diabetic foot ulcer

**Running title: Effect of superoxide solutions on diabetic ulcers**

## **Authors:**

- 1. Bhupinder Singh Walia, MS** (General Surgery), Associate Professor, Department of Surgery, Government Medical College, Amritsar, Punjab, India
- 2. Pankaj Dugg, MS** (General Surgery), Assistant Professor, Department of Surgery, Government Medical College, Amritsar, Punjab, India
- 3. Navjot Singh, MS** (General Surgery), Senior Resident, Department of Surgery, Government Medical College, Amritsar, Punjab, India
- 4. Sanjeev Sharma, MS** (General Surgery), Professor, Department of Surgery, Government Medical College, Amritsar, Punjab, India
- 5. Babu Lal Sunkaria, MS** (General Surgery), Professor (Retired), Department of Surgery, Government Medical College, Amritsar, Punjab, India

## **Corresponding Author:**

**Dr Pankaj Dugg**

Assistant Professor, Department of Surgery, Government Medical College, Amritsar, Punjab, India

E mail: dr\_dugg@hotmail.com

## **Abstract:**

**Introduction:** Diabetic foot and diabetic ulcers are common complications of diabetes mellitus. It affects daily life of patients and lead to amputations. The study was conducted to see the effect and role of superoxidised solution and gel (microdacyn) in promoting the healing and treatment of diabetic foot ulcer.

**Material & Methods:** The wound site was cleaned with normal saline followed by application of superoxidised solution for 30 seconds and then followed by application of wound care hydrogel. Observations were made during dressing and examination of the patients/ wounds was done on the day 7,14,21,28 and at follow-up of 15 days. Rate of contraction of wound is measured in  $\text{cm}^2$ .

**Results:** Mean age of patients in the study was  $50.0687 \pm 11.85$  years with equal male to female ratio. Superoxidised solution provides good wound healing and mean hospital stay was  $10.49 \pm 4.24$  days. Significant reduction of wound is seen in cases with short duration of ulcer and short duration of diabetes ( $p < .05$ ).

**Conclusion:** Superoxidised solution was associated with faster healing of ulcers without any major complications, proving SOS to be safe and efficient as a wound care product in the management of lower limb ulcers.

**Key words:** Diabetes mellitus, Wound healing, Superoxides, Ulcer

**Introduction:**

Diabetic foot is one of the main complications of diabetes that has known to affect day to day activities of the affecter. 85% of foot amputations and 70% of leg amputations has been known to be preceded by foot ulcers in diabetic patients.[1,2]

According to WHO lower limb amputation is being done every 30 seconds in world out of which 50% could be prevented by basic medical education and awareness among diabetics.[3] Major source of morbidity in individual with diabetes mellitus are also foot ulcer and infection. The risk of lower extremity amputation is 15 fold higher in diabetic as compared to non-diabetes.[4]

Multiple contributing causes has been known to cause diabetic foot ulcers which includes peripheral neuropathy, ischemia from peripheral vascular disease and immunopathy. Also mechanical stress normally associated with weight bearing, make the lower extremities particularly vulnerable to development ulcers.[4]

The various modalities used in treatment of diabetic foot ulcer includes dressing, debridement and antiseptics. Diabetic ulcers are known to be resistant to conventional treatment and may herald severe complications if they are not managed wisely. An ideal antiseptic is one that is rapidly lethal to all forms of bacteria and their spores, capable of bactericidal property for a prolonged period with no ill effect on host tissues. Superoxidized solutions (SOS) have emerged as one of the options for diabetic foot ulcers.[5]

The concept is formation of hypochlorite / hypochlorous species, free radicals are formed. There is generation of high reactive species of chloride and oxygen that rapidly react and denature proteins of bacterial cell wall with anti-inflammatory effects. Host tissues are spared as multicellular organisms are not prone to such osmolarity changes henceforth, it is host friendly.[6]

Use of Super Oxidized Solution in acute and chronic wounds was approved by European CE KEMA- Medical Device Class IIb (in 2004), and FDA (in 2005).[6,7,8,9,10]

As diabetic ulcers are a very common complication of diabetes mellitus and is burden on the Healthcare system therefore the present study was planned to study the effect of superoxidised solution with neutral pH (microdacyn solution and hydrogel) on diabetic pressure ulcers.

**Material and Methods:**

Fifty cases having diabetic foot ulcers presented to surgery department from Nov 2017 to Nov 2020 were taken up for study. Permission from institutional ethics committee was taken. Informed consent were taken from each and every patient prior to the start of the study.

The wound site was cleaned with normal saline followed by application of superoxidised solution for 30 seconds and then followed by application of wound care hydrogel. The solution was applied in form of spray and the hydrogel is applied by a pump. The antibiotics were given only after culture and sensitivity testing from wound. Observations were made during dressing and examination of the wound was done on the day 7,14,21,28 and at follow-up of 15 days.

The initial wound area (IA) was recorded by measuring length & breadth on day 1. The area of the target ulcer was measured by planimetry using transparent graph sheet.

Final wound area (FA) is area measured after 28 days of healing period. The formulae used to calculate % reduction in area of ulcer after 28 days was:

Rate of contraction of wound after 28 days =  $\frac{[\text{Initial area (IA)} - \text{Final area (FA)}]}{\text{Initial area (IA)}} \times 100$

**Eligibility criteria:**

Ages: 18 Years and older

Sexes: All

Sampling Method: Non-Probability Sample

Study Population

50 diabetic foot ulcer (DFU) adult male or female subjects, 18 years of age or over, with current or recent (within last six months) neuropathic foot ulcers were recruited.

**Inclusion Criteria:**

- Adult male or female, 18 years of age or over
- Has a diagnosis of type 1 or 2 diabetes
- Currently receiving treatment for a diagnosis of diabetic foot ulcer (DFU) or have had an active foot ulcer healed within the last 6 months
- Is not currently enrolled in a clinical trial for DFU
- Is willing and able to provide informed consent indicating that they understand the purpose and procedures required for the study
- Is willing and able to participate in the study which includes a 60 minute interview
- Willing to have interview audio-recorded
- Speaks English, Punjabi or Hindi as primary language

**Exclusion Criteria:**

- Subjects who does not meet the inclusion criteria
- Has diagnosis of critical limb ischemia
- Has ulcers that have exposure of tendon, bone, or joint capsule (Wagner grade >2)
- Has osteomyelitis or gangrenous ulcers
- Is currently enrolled in a clinical trial for DFU
- Is unwilling or unable to sign an informed consent document indicating that they understand the purpose and procedures of the study
- Is unwilling or unable to participate in the study which includes an interview of up to 60 minutes in duration

Statistical analysis was done using SPSS software windows version 19. Multivariate analysis was done using Chi square test with  $p < .05$  taken as level of significance. Mean and standard deviations were calculated on Microsoft excel 2016.

**Results:**

In our study maximum males (n=8) were present in age group of 51-60 years while maximum females were seen in age groups of 41-50 years and 51-60 years (n=7). Mean age of all patients were  $50.0687 \pm 11.85$  years while males and females had mean age of  $48.5266 \pm 12.59$  and

51.65981±11.16 years respectively. However there is not much difference in gender distribution (Table 1).

It was seen that 62 % of diabetic foot ulcers occurred on plantar aspect and 38 % on dorsal aspect of the foot (Table 2).

In our study 90% of patients had duration of diabetes upto 5 years and 10 % of patients had diabetes of > 5 years duration with majority of patients having Type II DM (n=33). However difference was not significant (p value .339354) (Table 3).

Mean hemoglobin was 10.48±1.54 gm%, mean fasting blood sugar was 146±23.58 mg/dl, mean serum creatinine levels were 1.12±0.47 mg/dl and lastly mean blood urea was 40.72±17.76 mg/dl (Table 4).

In our study 35 (70%) of patients had 7-14 days duration of hospital stay while only 1 case (2%) had a long >21 days duration of hospital stay. Mean duration of hospital stay was 10.49±4.24 days (Table 5).

Significant reduction in area of ulcer was seen in patients having ulcer of less than 3 months duration (p value .019983) (Table 6).

Patients having history of diabetes of less than five years have better chances of healing of ulcer (p value .000586) (Table 7).

The mean area of ulcer (in cm<sup>2</sup>) in study group was 25.92±6.50 on day 1, 23.10±5.95 on day 7, 20.10±5.54 on day 15, 16.63±4.53 on day 21 and 12.59±4.46 on day 28 respectively. A gradual decrease in area of ulcer was observed in our study from day 1 till day 28 (Fig 1). Reduction of 51.43% was seen compared to day 1.

### **Discussion:**

Etiopathogenesis of diabetes is mainly hereditary and environmental and it is considered one of the serious chronic illness. The incidence of lower limb complications in people with diabetes is increasing both in developed and developing countries of the world making it a major health concern.[11]

Polymicrobial infections mostly predominate in severe diabetic foot infection and include a variety of aerobic gram-positive cocci, gram-negative rods and anaerobes otherwise aerobic gram-positive cocci are the predominant pathogens in diabetic foot infections. The corner stone of management of diabetic foot ulcer were debridement, meticulous wound care and antibiotics. However need for novel approaches to diabetic wounds was felt due to emergence of MRSA and other resistant bacterial strains.[12,13,14] Demonstration of novel dressings put a major breakthrough for diabetic foot ulcer management over the last decades. In present scenario the ideal dressing should confer moisture balance, protease sequestration, growth factor stimulation, antimicrobial activity, oxygen permeability, and the capacity to promote autolytic debridement that facilitates the production of granulation tissues and the re-epithelialization process. In 2003 superoxide solutions came as relatively a new concept in wound dressing. Comparatively, the literature available on superoxidised solution is minimal in comparison to povidine iodine which is most commonly used. The action of superoxide solutions on antiseptics, faster wound healing and their non-irritable nature have prompted more people to use this solution for dressing

diabetic foot ulcers. Therefore in the present study we also used superoxidised solution to evaluate its efficacy in diabetic foot ulcers.

In this study, we present our findings on use of superoxide solution for 30 seconds and then followed by application of wound care hydrogel on fifty cases of diabetic foot ulcers. Our result show that maximum patients were in the age group of 51-60 years (n=15) with equal sex distribution. Mean age of patients were  $50.0687 \pm 11.85$  years (Table 1). Sridhar et al[15] reported mean age of patients to be  $56.4 \pm 18.6$  years with male predominance. Similarly Hadi et al[10] reported male to female ratio of 43:7 but mean age of the patients was  $40 \pm 11$  years. However Hardikar et al[16] reported diabetic foot was common between age group of 51-60 years with mean of  $54.7 \pm 9.0$  years which is in comparison of present study. This variation in results can be explained on the basis of population visiting the hospital and the geographical area to which they belong.

It was observed that 62 % of diabetic foot ulcers occurred on plantar aspect while only 38 % on dorsal aspect of the foot (Table 2). This observation is consistent with a similar findings by Edmonds et al[17] where majority of ulcers were seen on plantar aspect. Further, Sridhar et al[15] observed great toe being the most common site of diabetic foot ulcers in their study. Younis et al[18] reported that plantar surface ulcers were 61% and dorsal surface ulcers were in 31% of cases.

It was seen that majority of diabetic foot ulcers were seen in type 2 diabetics (n=33) while only 17 cases (34%) had type 1 diabetes (Table 3). Thus type 2 diabetics are more prone in developing diabetic foot ulcers. Our results are in agreement with the study of Zhang et al[19] in which he mentioned that the global prevalence of diabetic foot ulcer was 6.3% with higher prevalence in type 2 diabetes. Also 90% of our patients presented with a not much longer duration of history of diabetes which was upto 5 years while only 10 % of patients had history of diabetes of more than 5 years duration. 90% of the patients with diabetic foot ulcer had less than 5 years of diabetic history in our study. Boyko et al[20] in his study show no relation of duration of diabetes with ulceration.

It was observed that mean area of ulcer gradually decreased in study group on comparison from day 1 ( $25.92 \pm 6.50$ ) till day 28 ( $12.59 \pm 4.46$ ) with significant reduction (51.43%) as compared to day 1 (Figure 1,2). In similarity to ours Sridhar et al[15] also reported decrease in size of ulcer with the superoxide solution treated group was more. Kapur et al[21] also reported 70% reduction in wound size with superoxide solution, but Satishkumar et al.[22] noted reduction of 56%. Although the percentages vary in these studies, the general trend is consistent that superoxide solution produces faster wound healing. Kapur et al[21] showed early granulation and epithelization and earlier resolution of periwound erythema and edema with superoxide solution when compared to povidine iodine (PI) group at a mean follow up of 21 days. These results are comparable and similar to the results of our study. Paola et al[9] in a study reported a mean healing time was lower in the superoxide solution group than povidine iodine group that is  $45 \pm 14$  days and  $58 \pm 20$  days respectively.

The mean hospital stay of the patients were  $10.49146 \pm 4.24$  days (Table 5). Also percentage area reduction in wound size was significantly associated with factors like duration of ulcer and duration of diabetes which implies that ulcers of shorter duration healed faster as compared to ulcers of longer duration of onset (p value .019983)(Table 6) and healing is better when duration of diabetes is less (Table 7). However, Martínez-De Jesús et al[23] show no significant relation of duration of ulcer and duration of diabetes to wound healing.

Gutierrez studied various applications of superoxidised solutions and he concluded that superoxidised solution made it a good choice for wound care management because of the moistening effects and minimum toxicity found with the use of this solution. Also being a non-antibiotic technology it appears to offer a broad new paradigm for the prevention and treatment of acute and chronic wounds.[24]

### **Conclusion:**

In the present study there was faster healing of ulcers treated with superoxidised solution without any major complications. Ulcers of shorter duration and diabetes of less duration are factors that enhance ulcer healing. Superoxidised solution is safe and effective wound care product in the management of diabetic foot ulcer.

**Acknowledgements:** None

### **References:**

1. International Working Group on the Diabetic Foot. International consensus on the Diabetic Foot. 1999.
2. Boucher P, Teasdale N, Courtemanche R, Bard C, Fleury M. Postural stability in diabetic polyneuropathy. *Diabetes Care* 1995 May;18(5):638-45.
3. Meeral SS, Tamilselvan N, Satheeshkumar P. A Comparative Study of efficacy of Superoxidized solution against Povidone Iodine in the treatment of Diabetic Foot Ulcers. *IOSR J Dent Medi Sciences*, 2016 august;15(8):10-14.
4. Most RS, Sinnock P. Epidemiology of lower extremity amputation in diabetic individual. *Diabetes Care*.1983;6(1):87-91
5. Armstrong DG, Lavery LA, Nixon BP, Boulton AJ. It's not what you put on, but what you take off: techniques for debriding and offloading the diabetic foot wound. *Clin Infect Dis* 2004;39:S92-S99
6. Pandey PK, Koushariya M, Shukla S, Das S. Outcomes of Superoxide solution dressings in surgical wounds: a randomised case control trial. *International journal of Biological Medical Research* 2011;2(4): 965-68
7. Bongiovanni CM. "Superoxidized Water Improves Wound Care Outcomes in Diabetic Patients Nonhealing wounds are affected by opportunistic infection — perhaps the most difficult factor to overcome in any wound care setting." (2006).
8. Martinez-Munive A, Menedez-Skertchly A, Toiber M. Superoxidized water (Microcyn 60) for mesh hernioplasty in grossly contaminated fields: an experimental study. SE 163. Presented at the American- College of Surgeons, 91st Annual Congress in San Francisco, California. 2005: p.16-20.

9. Paola D, Brocco E, Senesi A. Use of Dermacyn: a new antiseptic agent for local treatment of diabetic foot ulcers. *J Wound Healing* 2005;2:201.
10. Hadi SF ,Khaliq T, Bilal N, Sikandar I, SaaiqM, Zubair M et al. Treating Infected Diabetic wounds with Superoxidised water as antiseptic agent: A preliminary experience –JCPSP 2007, VOL. 17 (12): 740-43
11. Powers AC, Niswender KD, Rickels MR. Diabetes Mellitus: Management and Therapies. In:Longo DL, Kasper DL, Jameson JL, Fauci AS, Hauser SL, editors.Harrison's Principles of Internal medicine. 18thed. New York:McGraw-Hill Professional Pub;2011. p.2968- 3002
12. Mulder GD. Diabetic foot ulcers: old problems-new technologies. *Nephrol Dial Transplant.* 2001;16:695-98.
13. Papanas N, Maltezos E.Becaplermin gel in the treatment of diabetic neuropathic foot ulcers. *Clin Interventions in Aging.* 2008;3(2):233-40.
14. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 1993 Feb;36(2):150-4.
15. Sridhar S, Nanjappa N. Microbiological and clinical response of superoxidized solution versus povidone iodine in the management of lower limb ulcers. *Natl J Physiol Pharm Pharmacol* 2017;7(10):1074-1080
16. Hardikar JV, Reddy YC, Bung DD, Varma N, Shilotri PP, Prasad ED, et al. Efficacy of Recombinant Human Platelet-Derived Growth Factor (rh-PDGF) Based Gel in Diabetic Foot Ulcers: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study in India. *Wounds.* 2005;17 (6):141-152.
17. Edmonds M. European and Australian Apligraf Diabetic Foot Ulcer Study Group. Apligraf in the treatment of neuropathic diabetic foot ulcers. *Int J Low Extrem Wounds.* 2009;8(1):11-8.
18. Younis BB, Shahid A, Arshad R, Khurshid S, Ahmad M, Yousaf H. Frequency of foot ulcers in people with type 2 diabetes, presenting to specialist diabetes clinic at a Tertiary Care Hospital, Lahore, Pakistan. *BMC EndocrDisord.* 2018;18(1):53.
19. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and metaanalysis. *Ann Med.* 2017;49(2):106–116.
20. Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer. The Seattle diabetic foot study. *Diabetes Care.* 1999;22(7):1036–1042.
21. Kapur V, Marwaha AK. Evaluation of effect and comparison of superoxidised solution (oxum) v/s povidone iodine (betadine). *Indian J Surg.* 2011;73(1):48-53.
22. Satishkumar R, Narayanaswamy T, Madhushankar L, Nikshita N. Superoxidised solution in the management of lower limb ulcers: Our experience. *J Evol Med Dent Sci.* 2013;2(44):8483-9.

23. Martínez-De Jesús FR, Ramos-De la Medina A, Remes-Troche JM, Armstrong DG, Wu SC, LázaroMartínez JL, Beneit-Montesinos JV. Efficacy and safety of neutral pH superoxidised solution in severe diabetic foot infections. *Int Wound J.* 2007 Dec;4(4):353-62. doi: 10.1111/j.1742-481X.2007.00363.x. Epub 2007 Oct 22. PMID: 17953678; PMCID: PMC7951458.
24. Gutierrez AA. The science behind stable super oxidized water exploring the various applications of super-oxidized solutions in clinical experience with a new and stable superoxidized water in wound treatment, advanced wound care with stable, superoxidized water. Supplement to January 2006 *Wound (A compendium of Clinical Research and Practice)*Page 7–10.

Tables:

TABLE 1: AGE AND GENDER WISE DISTRIBUTION OF CASES

AGE	Frequency		Total	Frequency
	Male	Female		
18-30	1	1	2	4%
31-40	5	3	8	18%
41-50	5	7	12	22%
51-60	8	7	15	30%
>60	6	7	13	26%
Total	25	25	50	100%
Mean±SD	48.5266±12.59	51.65981±11.16		
	50.0687±11.85			

TABLE 2: DISTRIBUTION OF ULCER ACCORDING TO SITE OF ULCER ON FOOT

Site	No. of cases	Percentage
Plantar	31	62%
Dorsal	19	38%
Total	50	100%

Table 3: DISTRIBUTION OF CASES ACCORDING TO TYPE OF DIABETES AND DURATION OF DIABETES

Duration	Type 1 DM	Type 2 DM	Total	Percentage
Upto 5 years	17	28	45	90%
>5 years	0	5	5	10%
Total	17	33	50	100%
P value	.339354*			

\*Chi square test  $p > .05$

TABLE 4: SHOWING VARIOUS HEMATOLOGICAL AND BIOCHEMICAL CORRELATION WITHIN STUDY POPULATION

Hematological parameters	MEAN VALUE±SD	Minimum value	Maximum value
Mean haemoglobin (gm%)	10.48±1.54	7.20	12.90
Mean fasting blood sugar (gm/dl)	146±23.58	110	198
Mean serum creatinine (gm/dl)	1.12±0.47	0.70	3.10
Mean blood urea (gm/dl)	40.72±17.76	20	96

TABLE 5: DURATION OF HOSPITAL STAY

Duration	Frequency	Percentage
<7 days	7	14%
7-15 days	35	70%
16-21 days	7	14%
>21 days	1	2%
Mean±SD	10.49146±4.24	

TABLE 6: SHOWING RELATION OF % AGE OF SIZE REDUCTION WITH DURATION OF ULCER

Duration of ulcer	Frequency	MEAN VALUE±SD Area of reduction	P value
Upto 3 months	40	55.93±11.14	.019983*
>3 months	10	36.28.±11.55	

\*Chi square test; p<.05 is significant

TABLE 7: SHOWING COMPARISON OF DURATION OF DIABETES (YEARS) WITH % AREA REDUCTION OF ULCER WITHIN STUDY POPULATION

Duration of diabetes (years)	Frequency	MEAN VALUE±SD Area of reduction	P value
Upto 5 years	45	54.22±11.16	.000586*
>5 years	5	32.00.±11.14	

\*Chi square test; p<.05 is significant

Figure 1: Reduction of size of ulcer in cm<sup>2</sup>

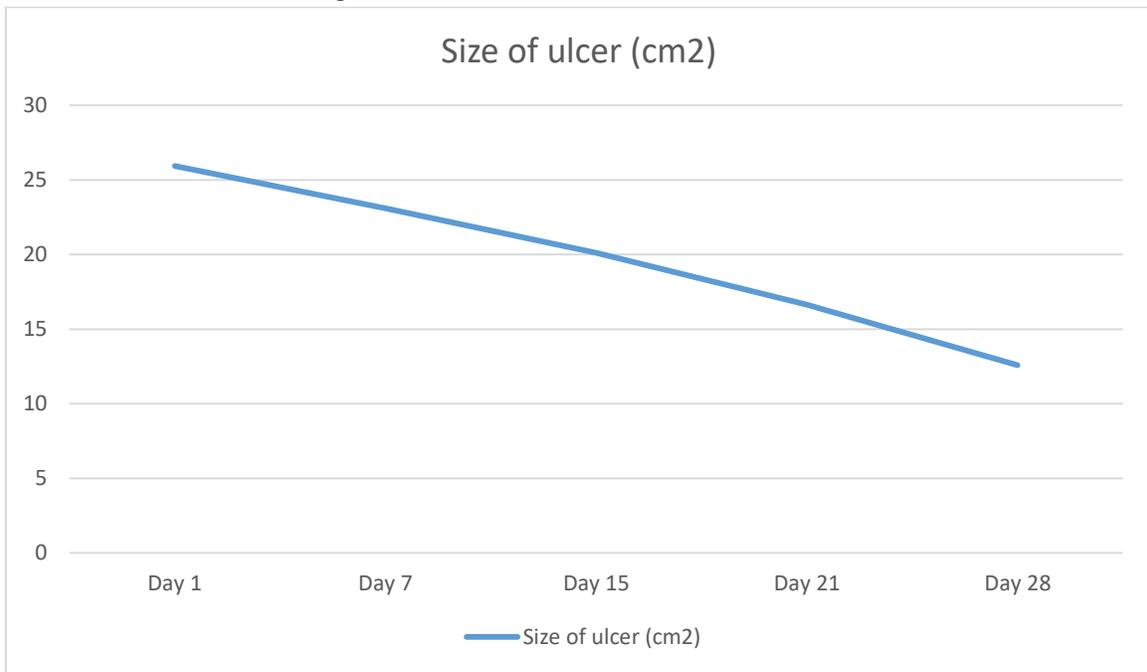


Figure 2: Ulcer from Day 1 to Day 28

