Research Analysis Report

Efficacy and Safety of Oxum in Treatment of the Venous Ulcer

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The present study was carried out to find out the efficacy and safety of oxum in the treatment of venous ulcers. The oxum (superoxidised water) is a pH neutral, non-irritating, aqueous solution that possesses a good antiseptic, antimicrobial activity and wound healing properties.

The study was conducted in 30 patients of venous ulcers with a culture examination positive for pathogenic microbial flora. All patients received a gauze dressing impregnated with oxum followed by compression bandage for 28 days. The primary endpoint was the calculation of ulcer size using ulcer tracing. Assessment of periwound oedema, periwound erythema, wound fibrin and wound granulations were considered as secondary endpoints.

There was a singificant reduction in ulcer size starting from day 7 of the treatment. Significant improvements in secondary endpoints were observed.

This study has demonstrated that oxum improved the clinical status, reduced the signs of inflammation in venous ulcers in addition to its well confirmed anti-infective properties.

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Key words : **Oxum, superoxidised water, venous ulcer, wound healing.**

Chronic venous ulcers affect 2% of the adult population in the western countries. Statistics are not available in India, but various reasons lead to the belief that the incidence may be higher[1]. Venous ulcers constitute majority of all leg ulcer, accounting for nearly 70% of chronic ulcers of lower limbs[2].

The most common causes of leg ulcers are venous insufficiency, diabetic neuropathy, and ulcers in ambulatory patients due to prolonged pressure and ischaemia. Other causes include trauma, infections, malignancy and metabolic conditions. Venous ulcers are also prone to infections. Incompetent veins or valves or an impaired muscle function may lead to abnormal calf muscle pump function leading to the elevation of the ambulatory venous pressure. This results in local venous dilatation and pooling, trapping leucocytes which release proteolytic enzymes destroying tissue. The venous pooling further induces inter-endothelial pore widening and deposition of fibrin and other factors which trap growth factors within them, rendering them unavailable for wound repair[3]. Typical ulcers present predominantly near the medial malleolus, are shallow, not too painful unless infected, and with a weeping discharge. They are frequently prone to infection.

There are many treatment modalities available, but compression bandages are the cornerstone of the venous ulcer therapy[4]. The aims are to keep the ulcer free of infection, absorb excess discharge, maintain a moist wound environment, supply adequate compression and promote venous drainage of the involved limb. Compression bandages reduce oedema of the surrounding tissue, reversing venous hypertension and improve the calf muscle pump function.

Venous ulcers have substantial economic effects in term of days of work lost. The chronicity also has an adverse effect on the patients' psychology, with depression and anxiety in large number of patients[4].

Technology has conquered many new frontiers in the past few decades. It has thrown up a new solution for the treatment of both chronic and acute venous ulcers; superoxidised water. Superoxidised waters are electrochemically processed aqueous solutions manufactured from pure water and sodium chloride. During this electrolysis process, molecules are pulled apart in a chamber with positive and negative poles, and hypochlorite/hypochlorus species and free radicals are formed, resulting in a mixture of reactive species of chlorine and oxygen. Oxum is a pH neutral, superoxidised water, which is non-toxic, non-irritating with a long shelf life of 12 months. It has been successfully utilised worldwide for the topical treatment of acute and chronic infective ulcers.

The present clinical trial is a single centre, prospective, study using oxum (superoxidised water) as a topical treatment for venous ulcers tested in 30 patients over one month.

MATERIAL AND METHOD

Thirty patients took part in the trial, where the safety and efficacy of oxum was evaluated in venous ulcers over a time period of 1 month.

The inclusion criteria included adults over the age of 18 years, with ulcers extending through the dermis and into subcutaneous tissue but without exposure of muscle, tendon, bone, or joint capsule, free of necrotic debris and with healthy vascularised tissue. Patients had to have adequate circulation to the foot as evidenced by a palpable pulse, wounds with a culture examination positive for pathogenic microbial flora with a relating antibiogram. The study was initiated after obtaining the written approval from the ethics committee. Patients clearly understood the purpose and methods of the trial and had given their written consent and were willing to follow-up for the trial duration.

The exclusion criteria included patients under the age of 18, pregnant or lactating women, intolerance to antibiotics or systemic anti-infective therapy suspected or proved. Ulcers of a non venous nature, with local ischaemia were excluded. Patients with clinically significant arterial diseases, need of immediate venous surgery, acute deep venous thrombosis as suggested by colour Doppler, history of bleeding disorder, traumatic or degenerative osteo-articular lesions in the lower extremity, presence of diabetes or any other systemic disease interfering with tissue repair and/or documented congenital or acquired immunity were omitted. Patients with malnutrition as documented by albuminaemia <2.0 g/dl, case history positive for drug dependency or alcohol abuse, schizophrenia or behavioural problems interfering with compliance or any other reasons for inability of compliance were also not considered. Presence of evidence of gangrene, cellulitis, osteomyelitis, or any other evidence of infection was checked and rejected. Patients receiving oral or parenteral corticosteroids, immunosuppressive or cytotoxic agents, coumarin, or heparin, antidiabetics, antihypertensives, diuretics and oral contraceptive agents were eliminated. Patients with reduction of motor or sensory faculties sufficient to compromise the patient's independence or with no family member or professionals available were left out.

A pretrial washout of 1 week was performed in all cases to establish stable baseline values. Each patient received a gauze dressing impregnated with oxum followed by compression bandage. After debridement, oxum was applied onto the wound in sufficient quantities to rinse the wound bed free of debris and then covered with gauzes soaked in oxum as the standard dressing. The dressing was held in place

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with a toe-to-knee elastic compression bandage.

Labelling of samples was done and the bottles containing the patient samples were numbered and the title of the study along with the dosage instruction to the patient.

The first, second, third and fourth visits were carried out at days 7, 14, 21, and 28 respectively. At these visits complete physical examination, concomitant therapy, clinical examination and assessment of the adverse effects were carried out. Laboratory tests including Hb, CBC, fasting and postprandial blood sugar, liver function tests like ALT, AST, alkaline phosphatase, bilirubin total and direct and renal function tests like BUN and creatinine were carried out.

The complete microbial investigation including the organisms found in the lesion along with their susceptibility to different antibiotics was done at the baseline and at the end of the study. The presence of deep vein thrombosis was ruled out by performing a colour Doppler examination.

A standard grading scale was laid down for the evaluation of the wound.

The primary efficacy endpoint was as follows — Ulcer tracings were done on a tracing grid. Whenever possible, the same person performed the tracing at every visit. The tracing was done after the wound has been debrided (with the exception of the screening/day 0 visit where pre and postdebridement tracings were to be performed). The acetate was placed onto the patient's wound. Using the sharpie, a direct tracing of the wound at the edge of the intact epithelium of the skin was taken. The acetate was removed from the wound. The patient's ID, patient's initials, date of tracing, initials of the person performing the tracing and the study time point was clearly recorded.

The ulcer wound area/size was calculated using the ulcer tracing. This was the primary efficacy endpoint.

The secondary efficacy endpoints were as follows — **Periwound erythema :** It is the congestive or exudative redness surrounding wound caused by engorgement of capillaries in lower layer of skin. It was graded as follows:

None (1) = Blanch on digital pressure

Mild (2) = Redness that does not blanch with pressure; may or may not be warm to the touch

Marked (3) = Prominent red or bluish colour; warm to touch

Periwound oedema : It is an excessive accumulation of tissue fluid in the tissue surrounding the wound. It was graded as follows:

None (1) = No observed signs of oedema

Mild (2) = Well defined oedema (edges of area well defined by defined by definite raising)

Marked (3) = Oedema raised by 1 mm or more

Wound fibrin : It is a yellowish – white meshwork not removable with a sterile swab or gauze. It adheres to the wound but can be removed with a blade by gentle scraping. It was classified as:

None (1) = No observed signs of fibrin

Mild (2) = A small amount of fibrin (< 50%) is present in the wound

Marked (3) = A large amount of fibrin (= 50%) is present in the wound

Wound granulation : It is a formation of small granular masses in the base of the wound that has a beefy- red appearance.

None (1) = No observed signs of granulation tissue

Mild (2) = Beginning to fill in and may not be epithelialised

Marked (3) = Epithelialising and filling in

Local adverse effects — The local adverse effects or signs of inflammation seen around the ulcer area were observed and noted. They were recorded at the baseline and all the visit days and described as either 'yes' or 'no' The local adverse effects to be considered were pain, irritation, redness, oedema and any other local adverse effects.

General assessment by the physician — This parameter was rated as good, satisfactory or poor by the physician at the end of the study period.

The following peripheral pulses were palpated:

Dorsalis pedis pulse in groove between first two tendons on medial side of dorsum of the foot.

Posterior tibial pulse as it curves forward, below and around the medical malleolus of the fibula.

Adverse events — The nature and severity of the adverse effects, if any, were recorded on the CRF.

Treatment failure — Patients who were not responding to therapy (no improved signs of ulcers healing even after 3 weeks of treatment) were to be considered as treatment failure and were to be removed from the trial and placed on alternative medication of physician's choice.

Concomitant treatment — Any other concomitant treatment like the use of antibiotic or analgesics was recorded in the case report form.

Data was computerised in EXCEL format from CRF. Student's paired 't' test was applied to the related data. All the tests were two tailed. Level of significance (alpha) was taken as $p < 0.05$

Observations

Thirty subjects with history of venous ulcer took part in the trial, of which 6 patients were female and rest were males. The average age of the study group was 45.67 ± 14.58 years. The average duration of the ulcer was 9.64 months. Of the study subjects 22 patients had ulcer on their legs, of which 9 patients had ulcers around the medial malleolus.

Primary end point — **Wound size :** At baseline the mean wound size was 213 ±303 ccm. The reduction in the score was significant right from the first visit onwards ($p<0.05$, mean ± SD) according to protocol. It was 172.73 ± 285.99, 133.77±250.56, 87.802±136.79 and 59.02 ± 111.59 ccm at the day 7, day 14, day 21, and day 28 respectively, which is a 18.92%, 37.21%, 58.79% and 72.3% reduction from the baseline percentage (Fig 1).

Secondary endpoint (Fig 2) — All the parameters assayed, except for fibrin, showed significant change, from the baseline. Fibrin change was significant from day 14 (second visit) onwards ($p<0.05$, mean ± SD).

Periwound erythema : At baseline the periwound erythema

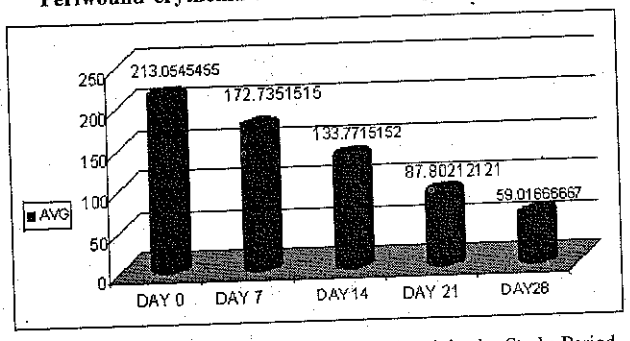

Fig 1 — Reduction in Ulcer Size Volume (ccm) in the Study Period

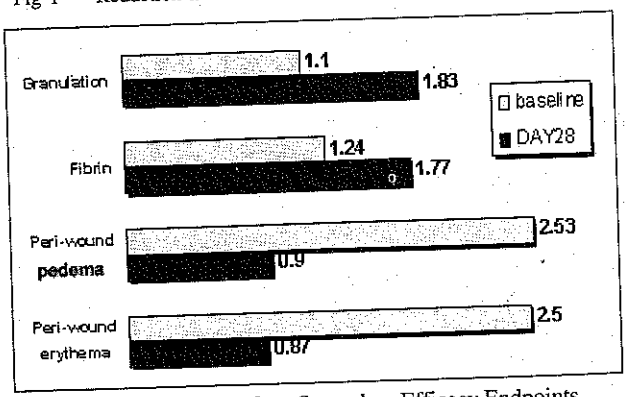

Fig 2 — Change in Mean Secondary Efficacy Endpoints

was 2.5 ±0.62. It was 1.97 ± 0.41, 1.67±0.47, 1.2±0.48 and 0.87 ± 0.5 on days 7, 14, 21, and 28 respectively, which is 21.33%, 33.33%, 52.0% and 65.33% reduction from the baseline value.

Periwound oedema : At baseline the periwound oedema was 2.53±0.62. It was 1.9 ± 0.40, 1.8±1.08, 1.23±0.5 and 0.9 ± 0.54 on days 7, 14, 21, and 28 respectively, which is 25%, 28.95%, 51.32% and 64.47% reduction from the baseline value.

Fibrin : At baseline the fibrin was 1.24±0.50. It was 1.37 ± 0.48, 1.73±0.63, 1.97±0.71 and 1.77 ± 1.28 at the Day 7, Day 14, Day 21, and Day 28 respectively, which is a 10.09%,39.63 %, 58.43% and 42.31% increase from the baseline value.

Granulation : At baseline the granulation was 1.1 ±0.3 It was 1.57 ±0.5, 2.03±0.48, 2.3±0.69 and 1.83 ± 1.21 on days 7, 14, 21, and 28 respectively, which is 42.42%, 84.85%, 109.09% and 66.67% increase from the baseline value.

Local adverse effects — Pain at the ulcer site : Twenty per cent of subjects had no pain at the baseline, whereas at the end of the study 100% of the subjects had no pain at the ulcer site (evaluated in 25 patients).

Irritation : Seventeen per cent subjects claimed no irritation at the baseline, which had increased to 75% at the end of the study (evaluated in 24 patients).

Redness : At the end of the study, 72% of patients showed no redness at the site of ulcer (evaluated in 25 patients).

Oedema : At the end of the study, 72% of patients did not show any evidence of oedema.

General assessment by the physician — The physicians evaluating the course of recovery of the patients, rated as follows,

Good - 65.52%, satisfactory - 31.03%, poor - 3.45%.

Discussion

Use of superoxidised water is a novel technological innovation in the therapy of venous ulcers. The oxum (superoxidised water) is a pH neutral, non-irritating, aqueous solution that posses a good antimicrobial properties activity against micro-organisms, including MRSA and VREF strains. It has an anti-allergic role to play by inhibiting Ig-E antigen induced granulation and cytokine release in mast cells by acting like a mast cell stabiliser[5]. This may have a role in venous ulcers as numerous mast cells are present in chronic venous ulcers[6].

Oxum triggers wound healing through fibroblast migration and proliferation , thus promotes tissue regeneration.

Oxum has been approved by USFDA, and regulatory authoritiesof UK, Italy, Germany, Singapore and Mexico as an effective method for wound care. Many studies have been conducted which have proved its efficacy and safety in diverse conditions such as diabetic foot ulcer, venous stasis ulcer, bed sores, burns, cuts, abrasions, postoperative infected wounds, cellulitis and abscesses[7-10]. In this study its effects are analysed in the Indian context.

The alteration in the primary and secondary efficacy endpoint along with the physicians' evaluation illustrates the action of oxum in venous ulcer care.

Primary endpoint : wound size — The change in the wound size reduction was significant from the 7th day onwards and nearly 72.3% reduction was witnessed at the culmination of the study (Fig 3)

Secondary efficacy endpoints — The periwound erythema and periwound oedema reduction was significant from the 7th day onward and showed a 65.33% and 64.47% change respectively from the baseline. At the same time the fibrin and granulation values were increased from 42.31% and 66.67% respectively from the first visit and found to be significant from the 14th and the 7th day onward respectively (Fig 4).

This favourable alteration in the efficacy endpoints reinforces the favourable clinical action of oxum. It has demonstrated a remarkable reduction in the common signs of inflammation like edema and erythema and remarkable increase in signs of healing of the ulcer ie, granulation and fibrin.

Local adverse effects — At the end of the study, there were no complaints of pain at the site of the ulcer in all patients. Seventy-five per cent of patients did not show any evidence of irritation, redness, oedema at the site of ulcer.

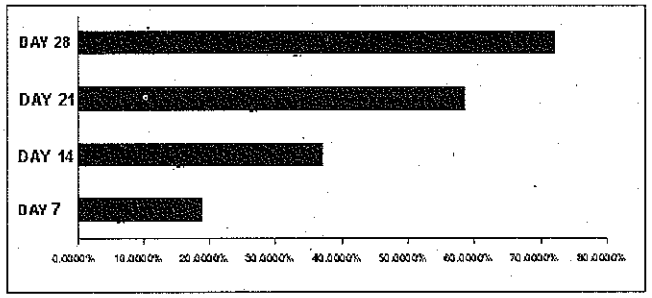

Fig 3 —Per cent Reduction from Baseline Seen in the Ulcer Size in the Study Period

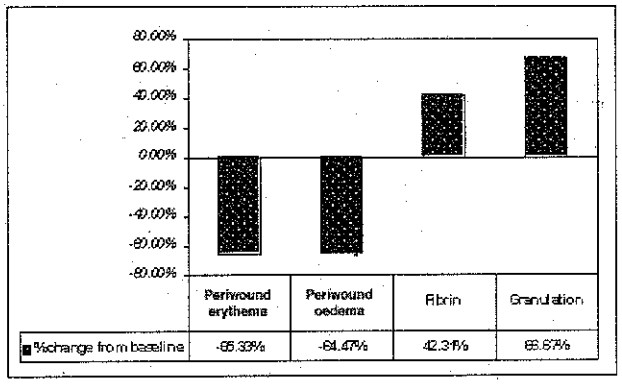

Fig 4 — Per cent Change from Baseline in the Secondary Endpoints

General assessment by the physician — As 65.52% of the physicians gave the treatment a good rating, it can be accepted that oxum even being a new approach in wound care in patients, was successful in winning the confidence of the treating physician (Fig 5).

At the end of the study 30% subjects showed no microbial load.

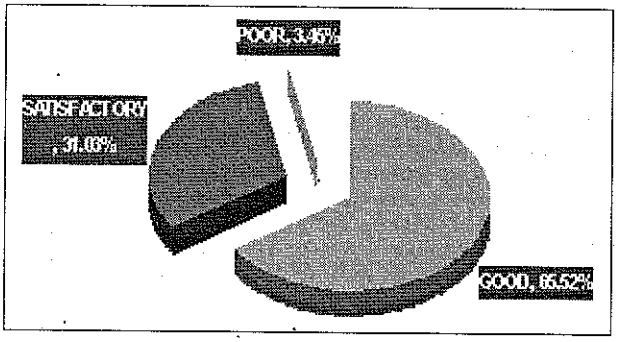

Fig 5 — General Assessment by Physicians

Oxum (superoxidised water) has been found to be effective against micro-organisms like *Staphylococcus aureus*, including MRSA and VREF, *E coli*, *Pseudomonas aeroginosa*, *Salmonella typhi*, bacillus atrophaeus spores and *Candida albicans* and virucidal against the human immunodeficiency virus and adenovirus[11]. Due to its broad-spectrum of antimicrobial action superoxidised water has been used as disinfectant for bronchoscopes[12] and dental units[13]. The bactericidal activity was similar to that of 80% ethanol, but superior to that of 0.1% chlorhexidine and 0.02% povidone iodine[14]. Oxum is active and safe in both animate and inanimate objects.

Oxum is mixture of the reactive species of both chlorine and oxygen. The action is due to a combined effect of reactive oxygen species and chlorine radicals. Its antispore activity is said to be by killing dormant spores by oxidatively modifying the inner membrane of the spores such that this membrane becomes non-functional in the germinated spore leading to its death. Similarly the biocidal properties of oxum are said to be by its effect upon constituents of the bacterial cell including proteins and nuclei acids[15], bringing about protein denaturation and cell wall lysis. Thus oxum will reduce the bacterial counts in the infected ulcers and improve wound conditions and fasten healing.

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