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Comparative Clinical Study of the Wound Healing Effects of a Novel Micropore Particle Technology: Effects on Wounds, Venous Leg Ulcers, and Diabetic Foot Ulcers

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Disclosure: Dr. Bilyayeva, Dr. Neshta, and Dr. Golub are inventors of Acapsil (Willingsford Ltd, Southampton, UK). Dr. Sams-Dodd is an employee of Willingsford Ltd.

Abstract: *Objective*. The purpose of this study was to determine the wound healing effects of Acapsil, a white, odorless powder based on micropore particle technology (MPPT) (Willingsford Ltd, Southampton, UK) by comparing it to Gentaxane (Gentaksan, Borshchagovsky CCP, Kyiv, Ukraine) (polydimethylsiloxane powder with gentamicin antibiotic) and Ioddicerin (Farmak, Kyiv, Ukraine) (iodine with dimethyl sulfoxide [DMSO]). *Materials and Methods.* The study included 266 patients with primarily trophic ulcers caused by pancreatic diabetes and venous insufficiency of the lower extremities, carbuncles, phlegmons, infected third- or fourth-degree heat burns, and infiltrations of postoperative wounds. The products were applied once daily to the wound until it was clean (ie, free from necrosis, pus, and fibrinogenous thickenings). *Results.* The number of days (mean ± standard deviation) to a clean wound was 3.0 ± 0.9 for MPPT (n = 88) compared with 7.0 ± 1.2 and 8.0 ± 1.1 for Gentaxane (n = 90) and iodine/DMSO (n = 88), respectively. Thus, MPPT reduced the time to reach a clean wound by 57% and 62%, respectively. Products were used once daily until a clean wound was reached, which also reflects the number of applications. Days to onset of granulation for MPPT, Gentaxane, and iodine/DMSO were 4.5 ± 0.8, 9.2 ± 1.4, and 10.3 ± 1.5 days, respectively; and days to onset of epithelialization were 7.8 ± 1.1, 14.1 ± 1.9, and 16.4 ± 2.7 days, respectively. Subgroup analysis of patients with diabetic foot and venous leg ulcers found that each of these demonstrated the same pattern of healing as the overall study. The number of hospitalization days was 14.6 ± 5.6 for MPPT, 21.0 ± 10.7 for Gentaxane, and 24.0 ± 7.9 for iodine/DMSO. Compared with Gentaxane, patients receiving MPPT had a 31% reduction in hospitalization duration and a 39% reduction compared with iodine/DMSO. *Conclusion.* These findings demonstrate that MPPT represents a valuable new approach to wound care.

Key words: burn wounds, diabetic foot ulcers, infections, lower extremity wounds, surgical, ulcer

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Acapsil (Willingsford Ltd, Southampton, UK), a new first-in-class medical device for wound care, is a fine white powder for application to the wound surface where it absorbs and removes excess wound exudate. It is intended to support the closure of wounds by secondary and tertiary intentions. This powder is based on a novel micropore particle technology (MPPT) that absorbs exudate into a highly porous structure that transports the exudate away by capillary action to the upper surface of the MPPT layer, where it effectively evaporates the exudate due to a highly enlarged surface area. A proteolytic enzyme immobilized inside the particles on the pore walls prevents viscous wound exudate from blocking the pores and preventing capillary action. The MPPT autoregulates the moisture level on the wound surface: if excess exudate is present, capillary action starts and transports the exudate away for evaporation from the MPPT layer surface. This action automatically stops when the excess fluid is removed. Due to this mechanism, MPPT can be used on wounds with low to high levels of exudate. The MPPT does not cause overdrying of the wound surface, because the particles retain a certain amount of moisture within them and this ensures a slightly moist, but not wet, environment at the wound surface.

Applying the MPPT is user friendly and takes minimal time. First, the wound surface is cleaned with water or saline and gently dried. Next, a 1-mm to 3-mm layer of MPPT is applied to the entire wound surface, including wound edges. Due to its mode of action, MPPT should only be covered by a light permeable dressing that allows moisture to evaporate; for difficult-to-dress areas, a secondary dressing can be omitted. The product does not have any debriding action, and eschar and larger areas of necrotic tissue should be removed prior to application; it will support autolytic debridement. Hydrogen peroxide (3%) can be used to assist the cleaning of the wound surface initially if needed. Micropore particle technology should be used until achieving a clean wound surface, ie, free of necrosis, pus, and fibrinogenous thickenings. For most wounds, a daily application for 1 to 5 days (average of 3 applications) is sufficient. Since MPPT is not absorbed, it can be rinsed off at any time with water or saline. Micropore particle technology can remain on the wound after the last application and will simply fall off as wound healing progresses.

A wound normally will progress through the inflammatory and proliferative phases of the healing process and proceed toward closure. However, the wound healing process may stall in the inflammatory phase (eg, due to infections or excessive inflammation) and can remain in this state for extended periods of time. Scientific and clinical data indicate[1] that once the wound is clean (ie, free of critical colonization and inflammation[2]), the wound will exit the inflammatory state and the healing process will proceed at its natural pace. This consequently means the primary goal of wound care should be to promote a clean wound, as this is the most important factor in determining overall time to wound closure. A number of clinical studies have supported this by demonstrating that time to reach the early stages in the healing process is predictive for overall time to wound closure.[3]

Previously, MPPT has been evaluated in a preclinical animal model[4] using the veterinary version of the MPPT product (SertaSil; Willingsford Ltd, Southampton, UK). The purpose of the present study was to extend these findings to the clinical setting to perform an initial evaluation of MPPT's ability to support wound healing across a wide range of wounds to close by secondary intention.

Materials and Methods

The wounds were primarily trophic ulcers caused by pancreatic diabetes and venous insufficiency of the lower extremities, carbuncles, furuncles, infected third- and fourth-degree heat burns, and infiltrations of postoperative wounds.

All included wounds were exuding and critically colonized to infected with remaining necrotic tissue or slough. The comparators were therefore chosen to be Gentaxane, a gel-forming polydimethylsiloxane powder containing the antibiotic gentamicin (Gentaksan, Borshchagovsky CCP, Kyiv, Ukraine) and iodine in combination with dimethyl sulfoxide (DMSO), where the DMSO is used to improve tissue penetration (Ioddicerin; Farmak, Kyiv, Ukraine). Iodine has antimicrobial properties and is used for minor wound debridement. All products were applied once daily until the wound was clean (ie, the wound was free of necrosis, pus, and fibrinogenous thickenings). Measurements for all patients included time to reach clean wound stage, time to onset of granulation, time to onset of epithelialization, and number of hospitalization days from start of application until hospital discharge. In addition, for a subgroup of patients with acute infected wounds, the wound surface area was measured on days 1 (start of application), 5, 7, and 10.

Number of participants. The study included a total of 266 patients; eTable 1 shows the inclusion/exclusion criteria. For measurements of the wound surface area, each group included 30 patients.

Follow-up period. Patients were monitored during their hospital stay; minimum duration of monitoring was 10 to 15 days after the last application of the product.

Ethical permissions. The study was approved by the Ethical Board of the Shupik National Medical Academy of Postgraduate Education and the Ethics Committee at the Clinical Hospital of Zaporizhzhia Station in Zaporizhzhia, Ukraine, in accordance with Ukrainian laws. All patients provided oral and written informed consent prior to participation in the study and signed medical reports to indicate their agreement with the treatment protocol. The trial was conducted in accordance with Good Clinical Practice principles, with the Declaration of Helsinki, and with relevant Ukrainian legislation. The study was performed in accordance with the protocol, and no amendments were required.

Comparators. Comparators included Gentaxane and an iodine/DMSO combination. Gentaxane is polydimethylsiloxane powder containing the antibiotic gentamicin, L-tryptophan, and zinc sulphate (gentamicin 24 mg/g, L-tryptophan 14 mg/g, zinc sulphate 10 mg/g in polydimethylsiloxane *ad* 1 g). Gentaxane is used for treating wound infections, and it has been shown to promote wound healing.[5] The iodine/DMSO is a topical antiseptic containing 0.5% iodine, 30% dimexide (DMSO), and 69.5% glycerine. Iodine has bactericidal effects and is commonly used for minor wound debridement, while DMSO improves tissue penetration. The 3 products used herein are different in use and appearance, and it was not possible to blind the trial. To minimize observer bias, the end-points were chosen to be quantitative measures. All measurements were taken with daily dressing changes.

Patient allocation. The goal of the study was to evaluate the effects of MPPT across a wide range of wounds in an exploratory manner. It was therefore not possible to use a traditional randomization scheme in this study. Instead, patients were allocated based on wound type to treatment groups in a sequential manner as the order of patient hospital arrival can be assumed to be random and unlikely to introduce a systematic error.

The process began with patient arrival at the Clinical Hospital of Zaporizhzhia, where the patient's pathology was determined. If suitable for inclusion in the study (eTable 1) and the patient agreed to participate, the patient was placed into the group with the fewest cases of that wound type, ie, sequentially to ensure an equal number of cases (eg, foot ulcers) were present in each group and the distribution of age, sex, and concomitant pathology was equal in the 3 groups. Due to the small size of the hospital, it was not possible to recruit sufficient numbers of patients for the group of acute wounds measured for the wound surface area during the study period (goal was 30/group), and for that reason historical data were included for the Gentaxane (17 cases) and the iodine/DMSO (15 cases) groups to have equal numbers in each group. These patients were selected from hospital files based on primary pathology, concomitant diseases, and age with the primary pathology as the principal criterion. Patients were treated and evaluated under identical conditions and by the same doctors in connection with a similar unpublished study conducted internally. A statistical analysis confirmed that the findings were unchanged if the retrospective cases were omitted from the analysis.

Parameters. For all wounds, the number of days to reach the clean wound stage, onset of granulation, and onset of epithelialization were recorded. These measurements can be used across wound types as they are independent of any underlying pathology and initial wound size, thus allowing comparison across wound types.

For abscesses, carbuncles, and infected wounds, the study also recorded wound surface area to determine the rates of wound closure. This measurement, to be meaningful, requires that the wounds have the same underlying pathology and same initial size. Acute infected wounds with a surface area ranging from 5 cm^2 to 15 cm^2 were included, and the rate of closure was measured for the first 10 days. Polyethylene film was applied on top of the wound, and wound circumference was copied onto the film. Lengths of all sides were measured in centimeters. Data were entered into a computer program (Sigma ScanPro; Systat Software, Inc, San Jose, CA), and wound surface area was calculated.

Finally, health economic parameters were determined by recording the number of hospitalization days for each patient in the study from the start of treatment until the patient was discharged and could continue treatment at an outpatient clinic or at his/her own general practitioner. Calculating the number of days a patient requires a hospital bed (during hospitalization) is a simple and reliable indicator of the economic toll, as it is a key factor in determining the overall costs of wound care for hospital inpatients.

Wound healing stages (eFigure 1):

1. Clean wound: Wounds entering the study were in the suppurative necrotic phase, which consists of alteration and exudation stages and is characterized by the presence of necrotic tissues and purulent

contents, edema, and high-microbial seeding. Wounds were determined to have reached the clean wound stage when they were free from necrosis, pus, and fibrinogenous thickenings.

2. Onset of granulation: The granulation phase consists of wound cleansing, normalization of microcirculation and metabolic processes in tissues, and granulation formation. Wounds were determined to have reached this stage when the first presence of granulation tissue was detected.
3. Onset of epithelialization: In this stage, the wound shows stable progressive epithelialization and active reduction of size. Wounds were determined to have reached this stage when the first presence of young skin (ie, epithelial tissue growth) was detected.

Bacteriological measurements. For patients with carbuncles in the MPPT group, samples were taken and analyzed at the hospital laboratory. Due to costs, hospitals do not routinely perform this analysis; therefore, it was only performed for the MPPT group.

Adverse events. Adverse events (AEs) were collected at each inspection of the wound and included events spontaneously reported by the patient, reported by the patient upon questioning, and events directly observed. Abnormal laboratory values or vital sign abnormalities were recorded as AEs only if they were medically relevant (ie, symptomatic, requiring corrective treatment, leading to discontinuation, or fulfill a criterion for a serious adverse event [SAEs]). In the case of chronic diseases, if the disease is known and documented when the patient entered the study, only increased frequency or intensity of the episodes were documented as an AE.

Adverse events were evaluated and categorized based on their intensity as follows: 1) mild: awareness of sign or symptom but easily tolerated (acceptable); 2) moderate: discomfort interferes with usual activities (disturbing); and 3) severe: incapable to work or to perform usual activities (unacceptable). To distinguish severe AEs from SAEs, the term severe is used to describe the intensity of the event and does not necessarily need to be considered serious. The assessment of causality of an AE was based on the following considerations: associative connections (time or place), explanations related to the MPPT, presence of clinical or pathological characteristic phenomena, exclusion of other causes, or absence of alternative explanations.

All AEs related to the application of MPPT occurring during the study were reported. No SAEs occurred. The follow-up of the patient who had experienced an AE continued until resolution of the event. All withdrawals due to an AE were recorded.

Procedure. As the patient entered the hospital, wound type and any underlying pathology were determined. Patient then was approached with the purpose of the study and its implications were explained. If the patient agreed to participate and provided written informed consent, he/she was placed into a group based on the previously described randomization scheme.

Prior to start of application, carbuncles were opened surgically; for other wounds, surgical necrectomy was performed if needed.

For all patients, if the wound was coated with necrotic and purulent tissue, the perimeter was cleaned with 2.5% iodine solution and the wound itself with 3% hydrogen peroxide; surgical necrectomy was performed if required. Wound was washed with physiological saline solution. Treatment included either a 1-mm to 3-mm layer of MPPT, a 1-mm to 3-mm layer of Gentaxane, or a bandage laced with 3 mL to 5 mL of iodine/DMSO applied to the wound. The MPPT and the Gentaxane layers then were covered with a gauze dressing.

Wounds were cleaned and redressed daily. The 3 products were applied once daily to the wound surface and edges until the wound was clean (ie, free from necrosis, pus, and fibrinogenous thickenings). After removing the old dressing, the wound was rated and measured, and any AEs were recorded.

Further care after reaching a clean wound and termination of application consisted, if needed, of bandages with methyluracil ointment (Metiluracil; Darnitsa, Kyiv, Ukraine) (100 g methyluracil ointment contains 5 g methyluracil, 0.5 g MIRAMISTIN ["Infamed" LLC, Moscow, Russia], and adjuvants [propylene glycol, macrogol 400, proxanol 268, cetyl alcohol, stearyl alcohol, and water]). The ointment and bandages were applied every 24 hours either until full wound closure or until the formation of active granulations and marginal epithelialization (ie, active tendency to heal).

Criteria for withdrawal and discontinuation of subjects. The withdrawal and discontinution of treatment for the study patients included the patient's request to be withdrawn from the study, the development of any SAE that could be attributed to MPPT, and the development of any severe AE, which could be attributed to MPPT and could not immediately be remedied.

If a patient was withdrawn from the study, the date and reason were recorded. Any measurements originating from the patient remained part of the dataset.

Statistical analysis. Data were analyzed statistically by two-way analysis of variance (ANOVA) with Fisher's least significant difference post-hoc test using the program package Systat 8.0 (Systat Software, Inc, San Jose, CA). The level for statistically significant differences was $P = .05$.

Results

Study compliance. There were no deviations from the protocol. All data recorded during the study were included in the analysis, except the number of hospitalization days for 1 patient with a diabetic foot ulcer (DFU). The patient had to undergo amputation of the other leg and the number of hospitalization days reflect events unrelated to the study wound.

Patient demographics. The study included a total of 266 patients with one study wound each. eTable 2 includes patient demographic data, and eTable 3 shows the wound pathologies in each of the 3 groups. The wounds were primarily trophic ulcers caused by venous insufficiency of the lower extremities and diabetes, carbuncles, phlegmons, third- or fourth-degree infected heat burns, and infiltrations of postoperative wounds. The study wounds were generally severe and needed intervention of a surgeon. Most patients with DFUs had type 2 diabetes, and the majority had had a moderately severe to severe clinical course with diabetic fourth-degree angiopathy of the lower extremities and polyneuropathy; most DFUs were infected, with some showing signs of gangrene. Most of the patients with venous leg ulcers (VLUs) and DFUs had a history of ischemic heart disease, atherosclerotic cardiovascular disease, and hypertension. eTable 4 lists concomitant pathologies.

Adverse events. Micropore particle technology did not cause any serious adverse reactions. In 3 patients with wide open VLUs located on top of and exposing nerve fascicles (nerve bundles) and causing extensive pain, MPPT increased the level of pain and made it necessary to discontinue use after 2 applications in 1 patient and 3 applications in the other 2. After discontinuation and rinsing the wound with saline, the pain level immediately returned to its pre-application level. During the period it was used, MPPT was able to promote a clean wound. The data from these 3 patients are included in the analysis.

Micropore particle technology did not cause any other AEs, eg, allergy, contact sensitivity, wound irritation or pain, bleeding, or over-drying of the wound.

Cases of 3 patients in the MPPT group:

Case 1: thermal burn. A 59-year-old man was hospitalized at the Clinical Hospital of Zaporizhzhia with a 2-week-old thermal burn of the right thigh and shank, 4% total body surface area, third-degree burn. The state of the patient was moderate with 38.5°C body temperature, and the whole surface of the skin and subcutaneous basis in the affected area was necrotic with dense scab. Operative necrectomy was performed then MPPT was applied to the wound surface. The body temperature decreased 2 hours after applying the MPPT. Complete wound cleansing from necrotic masses took place over a 48-hour period. Besides MPPT, the patient received only anaesthetics and vascular agents as he was allergic to antibiotics of the most commonly used groups. Micropore particle technology was applied for 3 days. After the wound reached the clean stage of healing, bandages with methyluracil ointment were applied every 48 hours until complete wound closure. The wound closed 17 days after the first application of MPPT.

Case 2: gunshot wound. A 41-year-old man was admitted to the surgical department with a 2-week-old gunshot wound complicated with inflammatory infiltration of the anterior abdominal wall. On examination, an infiltration of 11.0 cm x 6.5 cm in the left iliac area was found. In the infiltration center was a bullet hole measuring 1.5 cm x 0.7 cm, with a wound channel located from the outside to the inside of the body measuring about 3.5 cm in length. Tissues around the wound channel were necrotic, swollen, and dark in color. At the bottom of the wound channel (inside the body), a bullet was found. The bullet was removed during surgery, and necrectomy was performed. Postoperatively, he received ceftriaxone 1.0 g twice daily intramuscularly for 5 days, sodium diclofenac 3.0 mL intramuscularly once daily for 3 days, lidase 64 units once daily intramuscularly and ultra high frequency field on the infiltration area for 7 days, and daily bandaging with iodine/DMSO and dioxysole. This performed treatment had no substantial effect; the infiltration retained its previous sizes, and no evidence of wound healing was observed. The patient outright rejected the proposed surgical treatment of excising the infiltration. It was decided to apply MPPT by administering it into the wound channel after cleaning it with 3% hydrogen peroxide. Micropore particle technology was applied for 2 days, and during this period the wound channel was completely cleared of necrotic masses. Over the following 7 to 8 days, the infiltration reduced to 3.0 cm x 2.5 cm, the wound channel was superficial, and the wound filled with granulations and was actively epithelializing. The wound healed completely and the infiltration resolved

14 days after the initial application of MPPT. At a 1-month follow-up, a surface scar measuring about 1.0 cm x 0.4 cm remained. The patient had no complaints.

Case 3: venous leg ulcer. A 70-year-old man was hospitalized and diagnosed with chronic venous insufficiency of the lower extremities complicated with trophic ulcers covered with patches of necrotic tissues. *Bacteroides fragilis* and *Escherichia coli* was identified (108 CFU/g) based on microbiological examination of tissue samples. After 2 rounds of dressing with MPPT, no microbes were obtained and the ulcer was completely clean in 3 days. Henceforth, methyluracil ointment was used for bandages until reaching wound closure 17 days after first application of MPPT.

Rate of wound closing. For patients with abscesses, carbuncles, and infected wounds, the wound surface area was measured at days 1, 5, 7, and 10 post application (eFigure 2). Each group included 30 patients, and the distribution of wound types was 80% carbuncles, abscesses, and cysts, and 20% infected wounds for all 3 groups. Overall, there was a significant difference between the groups over the time period (ANOVA with repeated measures $F[2,85] = 50.71$; $P < .001$). On day 1 of application, there were no differences between the groups; at days 5, 7, and 10, the patients receiving MPPT had significantly smaller wound surfaces compared to Gentaxane and iodine/DMSO.

Time to reach specific wound healing stages. The number of days to reach each of the 3 stages in the wound healing process and the number of hospitalization days were determined for all patients in the study (eTable 5; eFigures 3, 4). Days to reach the clean wound stage also reflected the number of applications for each of the 3 products as they were applied once daily until reaching a clean wound. This stage was achieved in 3.0 ± 0.9 days for patients receiving MPPT (n = 88) compared with 7.0 ± 1.2 days for Gentaxane (n = 90) and 8.0 ± 1.1 for iodine/DMSO (n = 88). Compared with Gentaxane and iodine/DMSO, the MPPT reduced the time to reach the clean wound stage by 57% and 62%, respectively. Days to onset of granulation for MPPT, Gentaxane, and iodine/DMSO were 4.5 ± 0.8, 9.2 ± 1.4, and 10.3 ± 1.5, respectively; the days to onset of epithelialization were 7.8 ± 1.1, 14.1 ± 1.9, and 16.4 ± 2.7, respectively. The number of hospitalization days was 14.6 ± 5.6 for MPPT, 21.0 ± 10.7 for Gentaxane, and 24.0 ± 7.9 for iodine/DMSO. Compared with Gentaxane, patients receiving MPPT had a 31% reduction in the number of hospitalization days and a 39% reduction in comparison with iodine/DMSO.

The analysis was repeated for the main wound types in the study (ie, wounds, VLUs, and DFUs), and they displayed the same pattern of healing (data not shown).

eTable 6 summarizes the hospitalization day reduction by MPPT compared with Gentaxane and iodine/DMSO for the main wound types in the study. Compared with Gentaxane, MPPT reduced the number of hospitalization days by 41% for wounds, 31% for DFUs, and 19% for VLUs.

eTable 7 summarizes the number of days between each of the different stages in the wound healing process. The data show that MPPT compared with Gentaxane and iodine/DMSO reduced the time to reach the clean wound stage as well as the time between the clean wound stage to onset of granulation and between onset of granulation to onset of epithelialization. In contrast, Gentaxane and iodine/DMSO had similar effects when compared with each other. However, as shown in the rightmost column of eTable 7, once the epithelialization had started, the time to patient discharge was very comparable across the 3 groups. Data are plotted for each group in eFigure 5, together with percentage reduction by MPPT relative to Gentaxane.

Microbiological analysis. Micropore particle technology was used in the treatment of 11 carbuncles. After opening the 11 carbuncles, 7 tested positive for *Staphylococcus aureus*, 1 for *Pseudomonas aeruginosa,* and for 3 an infective agent not identified. In all cases, MPPT assisted in closing the wound.

Discussion

The purpose of the present study was to provide initial clinical data on the ability of MPPT to support the healing of wounds to close by secondary intention. In this study, MPPT was compared with Gentaxane and iodine/DMSO. The study included a wide range of wounds, ulcers, and burns, and the products were used once daily until the wound was clean — ie, free of necrosis, pus, and fibrinogenous thickenings. The number of applications and the number of days to reach a clean wound were therefore the same.

The investigators found that to reach a clean wound, MPPT was used for 3.0 ± 0.9 days, Gentaxane for 7.0 ± 1.2 days, and iodine/DMSO for 8.0 ± 1.1 days. Therefore, the use of MPPT resulted in a 60% reduction in time to reach the clean wound stage compared with Gentaxane and iodine/DMSO, and consequently resulted in 60% fewer dressing changes. This reduction in time to a clean wound also led to reductions in time to reach the subsequent wound healing stages — onsets of granulation and epithelialization. Overall, the use of MPPT resulted

in a 31% reduction in the number of hospitalization days for patients when compared with Gentaxane and iodine/DMSO. The reduction in hospitalization days was 44% for wounds, whereas it was 19% and 31% for VLUs and DFUs, respectively.

Micropore particle technology did not cause any SAEs, and there were no cases of wound or skin irritation, allergy, contact sensitivity, increased bleeding, or other AEs. In 3 patients who had painful VLUs and where nerve fascicles were exposed, MPPT exacerbated the existing pain level, but upon rinsing the wound with saline, the pain level immediately returned to its baseline level. Subsequent experience has shown that this pain can be avoided by applying MPPT in a thinner layer on the exposed nerve fascicles. The cause of the pain is most likely an acute excitation of neurons in the exposed nerve due to the rapid absorption of fluid by the MPPT. Micropore particle technology is not absorbed by the body and nothing is released onto the wound surface, and it can therefore be removed completely by rinsing with water or saline. Consequently, MPPT was found to be safe for use in wound care.

Based on a review of clinical data, Thomas[1] found that the critical aspect of the wound healing process for wounds demonstrating delayed healing is to reach the state of a clean wound bed (ie, free from critical colonization and inflammation). Once this state has been reached, the healing process will progress and the rate of wound closure will occur at its own natural pace. In a review of 18 studies,[3] the authors found that a number of clinical studies have supported this by demonstrating the time to reach the early stages in the healing process is predictive for overall time to wound closure.

The present study found that MPPT, compared with Gentaxane, reduced the time to a clean wound by 60% and the time from a clean wound to the onsets of granulation and epithelialization by 32%. In contrast, the time from onset of epithelialization to patient discharge was constant (eFigure 7). These data support the theory by Thomas[1] that reducing the time to a clean wound has a substantial impact on the overall wound healing process, but the data also indicate the transition from the inflammatory to the proliferative wound healing phase is less distinct and MPPT also accelerates at least the early stages of the proliferative phase. The present study did not follow the individual wounds until closure and the actual duration of the complete proliferative phase is therefore unknown; however, MPPT reduced the time to onset of epithelialization by about 7 days compared with the patients receiving Gentaxane, and the patients who received MPPT were discharged 7 days earlier than those receiving Gentaxane. Thus, the data indicate that MPPT mainly achieved its effect by accelerating the transition from the inflammatory phase into the proliferative phase. The conclusion is supported by a preclinical study with this product, where an earlier presence of immune cells associated with the proliferative phase, ie, monocytes and lymphocytes, were seen in the MPPT group compared to the Gentaxane group and to the untreated controls.[4]

An entry criterion for the study was the presence of pus and fibrinogenous thickenings in the wound (ie, the presence of an infection or a critical colonization). Furthermore, bacteriological analysis of carbuncles in the MPPT group demonstrated the presence of different pathogenic bacterial strains. For all wounds that received MPPT, it was found that the wound progressed towards closure without further complications and without the specific need for antimicrobial treatment.

Preclinical data[4] have shown MPPT is not antimicrobial and does not inhibit the colonization of the wound, so the question is how does MPPT support the healing of infected or critically colonized wounds? Micropore particle technology is a powder and the powder format allows the product to spread into all crevices on the wound surface. Micropore particle technology acts as small micropumps, which suck away exudate from the wound surface through capillary action. Studies[6-8] have shown that some pathological bacterial strains release toxins that inhibit the immune system, and it is very likely that MPPT removes these toxins from the wound surface when removing the exudate, and thereby removes their inhibition of the immune system. Another key bacterial defensive mechanism against the immune system is the secretion of biofilm.[9,10] However, bacterial biofilm is composed of 90% to 95% water, and, due to its highly effective micro-pumping action, MPPT will also remove water from these structures. The particles in MPPT will touch the biofilm surface and will locally suck holes in the biofilm, disrupting the surface of the biofilm and exposing the bacteria to the immune cells. This effect on the structure of the biofilm has been confirmed in mature *P aeruginosa* biofilm cultures.[11] The micropumping action by MPPT will therefore remove toxins released by pathogenic bacteria and disrupt the biofilm layer, thereby effectively disabling the 2 main defensive systems bacteria use against the immune system. As a result, the immune system now can selectively kill the pathogenic bacteria while preserving the beneficial, natural colonization of

the wound. This now can spread to prevent the invasion of new pathogenic strains.

In comparison, antibiotics are indiscriminate in their action — more akin to saturation bombing — and will kill any bacteria, whether benign or pathogenic, sensitive to their effects. Once antibiotic treatment stops, the wound is poorly colonized and open to reinvasion by pathogenic strains, so the colonization of the wound becomes more a race than a process controlled by the immune system. An important benefit of MPPT is also that by enabling the immune system to fight the infection, any problems in relation to antibiotic resistance are circumvented, and, furthermore, the risks of creating new antibiotic-resistant strains are avoided altogether because no antibiotics are used.

Limitations

The goal of this study was to provide an initial evaluation of the value of MPPT in clinical wound care for the most common wound types to determine its potential medical benefits. Due to this wider aim, less detailed information was consequently obtained for specific wound types, and it is therefore important to extend this initial study with detailed studies of specific wound types (eg, acute versus chronic wounds, different DFU grades) to guide the optimal clinical use of MPPT. Similarly, the study did not collect data on a number of clinically important parameters, eg, pain which is likely to be affected by MPPT, as many patients spontaneously reported a reduction in wound pain and lower levels of pain associated with dressing changes.

Conclusion

In summary, the present study found that MPPT used on wounds, ulcers, and burns reduced the time to reach a clean wound by 60% compared with Gentaxane and iodine/DMSO; this led to a 31% reduction in the number of hospitalization days required until patients could be discharged and continue treatment with their general practitioner or at an outpatient center. Micropore particle technology achieves this by supporting the transition from the inflammatory phase into the proliferative phase, including the support of the immune system's ability to fight an infection, whereby the use of antibiotics can be avoided. Furthermore, MPPT was found to be safe to use in wound care.

This study represents an initial clinical evaluation of MPPT. However, the findings are robust, and replicate the findings of a previously published preclinical study[4] in an animal model and comparable effects have been observed during the use of MPPT in veterinary wound care and more recently by a UK hospital[12] on dehisced surgical wounds and pressure ulcers. Altogether, this indicates that MPPT offers a new, effective approach to wound healing.

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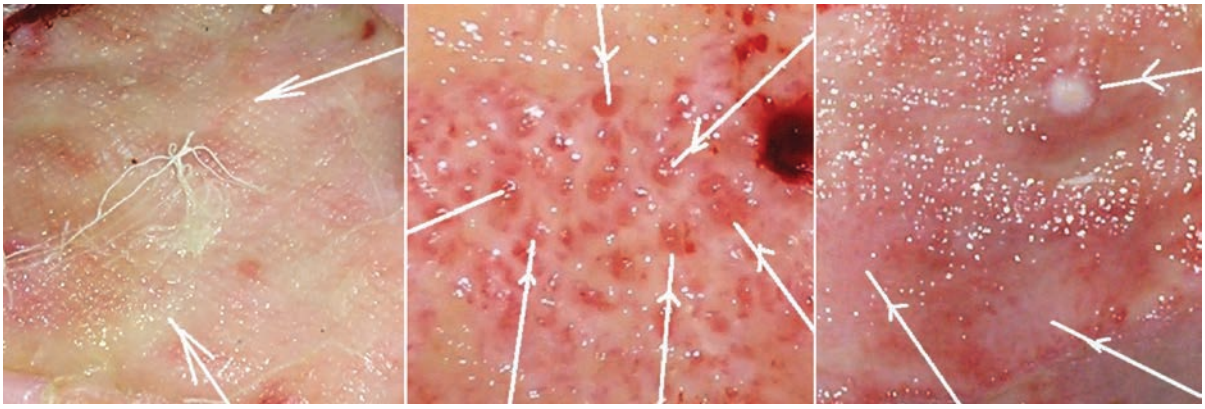
eTable 1. Inclusion and exclusion criteria	
Inclusion Criteria	• Age: ≥ 18 years • Gender: Males and nonchildbearing females • Presence of a wound that required intervention by a surgeon • Wounds included trophic ulcers caused by venous insufficiency of the lower extremities and diabetes, carbuncles, phlegmons, third- and fourth-degree infected heat burns, and infiltrations of postoperative wounds, but no limitations on the types of wounds that could be included • Patients with concomitant pathologies were included in the analysis and were allowed any required medication • Compliance: Understood and were willing, able, and likely to comply with all study procedures and restrictions • Consent: Demonstrated understanding of the study and willingness to participate as evidenced by voluntary oral- and written-informed consent
Exclusion Criteria	• Diabetic foot ulcers or venous leg ulcers having reached a stage where amputation was required • Patient was childbearing



Suppurative Necrotic Phase. Arrows indicate suppurative necrotic layers.

Granulation Phase. Arrows indicate early granulation tissue.

Epithelialization Phase. Arrows indicate early epithelial tissue.

eFigure 1. Close up of wounds at each of the 3 wound healing phases.

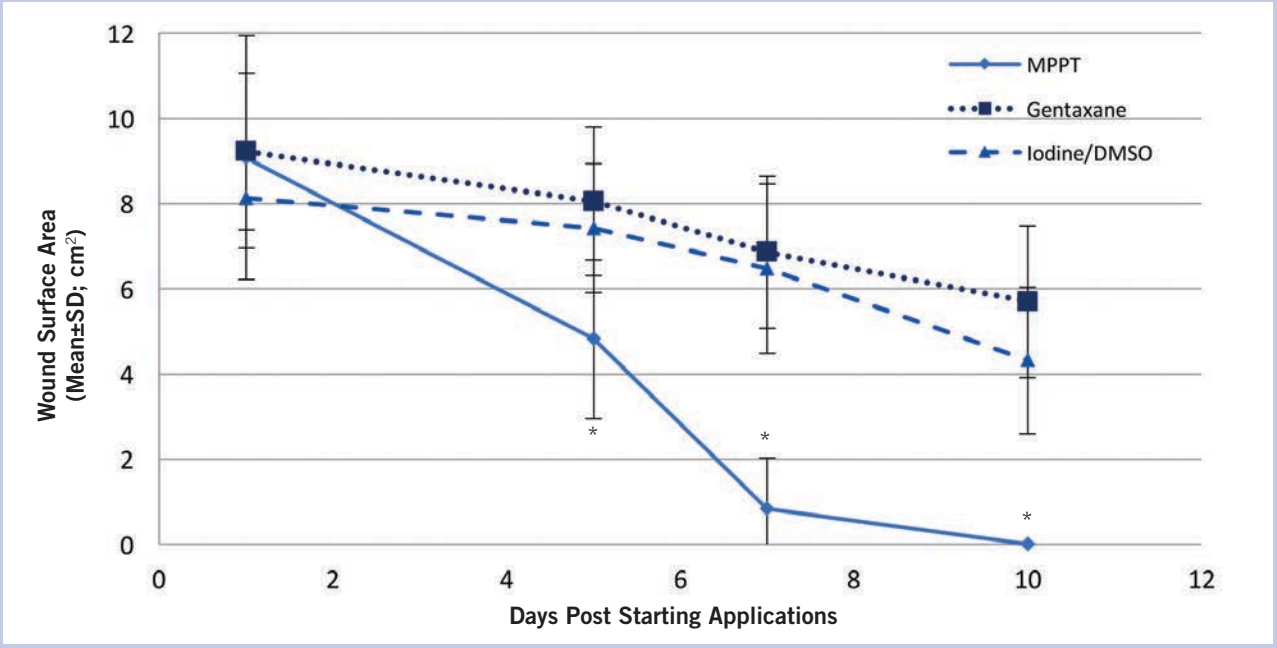
eTable 2. Patient demographic data			
Patient Demographics	**Treatment Groups**		
	MPPT	**Gentaxane**	**Iodine/DMSO**
Number of patients	88	90	88
Male:Female ratio	1:1.15	1:1	1:1.32
Age (mean±SD)			
Men	49.9±13.5	47.3±17.9	43.7±20.8
Women	54.8±17.7	58.8±16.7	54.9±19.4
Age range (y)	21–79	20–96	18–86
MPPT: micropore particle technology; DMSO: dimethyl sulfoxide; SD: standard deviation			

eTable 3. Types of wound pathologies treated			
Wound Pathology	**Treatment Groups**		
	MPPT	**Gentaxane**	**Iodine/DMSO**
Varix dilatation of lower extremities; trophic ulcers of lower extremities	20	18	16
Abscesses, furuncles, carbuncles	18	20	24
Pancreatic diabetes; diabetic foot syndrome	13	13	10
Phlegmons of soft tissues	6	7	4
Necrotic form of erysipelas	5	4	3
Infected wounds	4	5	6
Infected thermal third-degree and fourth-degree burns	3	3	2
Postinjection abscesses of small pelvis	3	4	2
Purulent paraproctitis	3	4	4
Festered coccyx cyst	2	2	3
Purulent sialadenitis	1	0	0
Osteomyelitis; sinus form	1 (radiation osteomyelitis of lower jaw)	0	2 (shin-bone fracture)
Gunshot wound in abdominal wall	1	0	0
Purulent elbow joint bursitis	1	0	0
Postradiation forearm ulcer	1	0	0
Purulent mastitis	1	0	1
Festered epidermal cyst capitis	1	0	0
Purulent hidradenitis	1	0	1
Festered atheroma	1	1	2
Suture purulent sinus in abdominal wall	1	2	1
Purulent prepatellar bursitis	1	0	0
Epidermal festered gluteal cyst	0	1	0
Sacrum bedsore	0	1	0
Festered cyst of neck	0	1	0
Felons	0	4	3
Other	0	0	4
Total	**88**	**90**	**88**
MPPT: micropore particle technology; DMSO: dimethyl sulfoxide			

eTable 4. Patient comorbidities			
Comorbidities (concomitant pathology)	**Treatment Groups**		
	MPPT (n=88)	**Gentaxane (n=90)**	**Iodine/ DMSO (n=88)**
Essential and/or symptomatic hypertension	28	19	23
Coronary heart disease	24	21	19
Circulatory insufficiency	17	18	18
Pancreatic diabetes	14	6	7
Kidney diseases	6	10	8
Arrhythmia	6	2	4
Cerebral atherosclerosis	5	3	5
Stenocardia	5	4	5
Obesity	5	3	1
Encephalopathy	4	2	4
Oncopathology	3	3	
Stomach ulcer and duodenal ulcer	3	3	2
Arthrosis	3	3	4
Anemia	4	3	-
Sensory deafness	3	1	2
Diabetic polyneuropathy of lower extremities	3	1	1
Hypothyroidism	1	-	-
Degenerative-destructive spinal pathology	1	1	-

eTable 4. Patient comorbidities (continued)			
Comorbidities (concomitant pathology)	**Treatment Groups**		
	MPPT (n=88)	**Gentaxane (n=90)**	**Iodine/ DMSO (n=88)**
Allergic dermatitis	1	1	-
Chronic nonobstructive inflammatory diseases of lungs (bronchitis)	1	-	1
Free abdominal hernias	1	-	1
Angioretinopathy	1	-	1
Erysipelas	-	2	-
Chronic pancreatitis	-	2	2
Prostatic adenoma, prostatitis	1	2	1
Pneumonia	-	1	-
Pathology of lympho-venous system of lower extremities	-	5	1
Chronic cholecystitis	-	1	1
Chronic gastritis	1	-	1
Paresis, paralysis	-	-	2
Cataract	-	-	1
Tonsillitis	-	-	1
Drug addiction	1	-	-
Closed craniocerebral injury	-	1	-
Gastrointestinal hemorrhage	-	1	-
Total	**142**	**119**	**116**

Some patients expressed several comorbidities for which reason the total number of pathologies exceeds the number of patients.
MPPT: micropore particle technology; DMSO: dimethyl sulfoxide

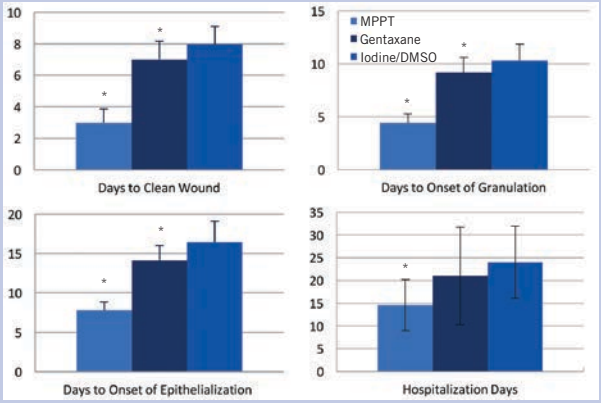


eFigure 2. Wound surface (cm^2) for days 1 to 10 following the start of treatment applications. Each group included 30 patients, and the distribution of wound types was 80% carbuncles, abscesses, and cysts, and 20% infected wounds for all 3 groups. N=30/group.
SD: standard deviation; MPPT: micropore particle technology; DMSO: dimethyl sulfoxide
* $P<.001$

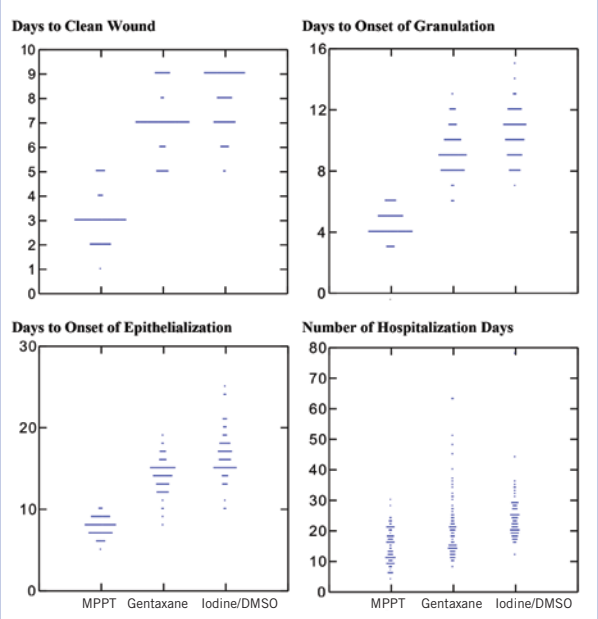
eTable 5. Wound stage measurements for all study patients

Mean±SD	Days to Clean Wound	Onset of Granulation	Onset of Epithelialization	No. of Hospitalization Days
MPPT	3.0±0.9	4.4±0.8	7.8±1.1	14.6±5.6
Gentaxane	7.0±1.2	9.2±1.4	14.1±1.9	21.0±10.7
Iodine/DMSO	8.0±1.1	10.3±1.5	16.4±2.7	24.0±8.0
ANOVA	F(2,263)=546.0; *P*<.001	F(2,263)=507.8; *P*<.001	F(2,263)=441.3; *P*<.001	F(2,262)=28.4; *P*<.001
MPPT vs. Gentaxane	57% reduction *P*<.001	52% reduction *P*<.001	45% reduction *P*<.001	31% reduction *P*<.001
MPPT vs. Iodine/DMSO	62% reduction *P*<.001	57% reduction *P*<.001	53% reduction *P*<.001	39% reduction *P*<.001
Gentaxane vs. Iodine/DMSO	12% reduction *P*<.001	11% reduction *P*<.001	14% reduction *P*<.001	12% reduction *P*<.05

MPPT (n=88); Gentaxane (n=90); or Iodine/DMSO (n=88)
SD: standard deviation; MPPT: micropore particle technology; DMSO: dimethyl sulfoxide; ANOVA: analysis of variance



eFigure 3. Days (mean±SD) to reaching the 3 wound healing stages in patients following application of MPPT (n=88), gentaxane (n=90), or iodine/DMSO (n=88).
SD: standard deviation; MPPT: micropore particle technology; DMSO: dimethyl sulfoxide
* *P*<.001



eFigure 4. Density plots for all 266 study patients. The graphs show days to reach the clean wound stage, onset of granulation, onset of epithelialization, and hospitalization days following application of MPPT (n=88), Gentaxane (n=90), or iodine/DMSO (n=88).
MPPT: micropore particle technology; DMSO: dimethyl sulfoxide

eTable 6. Percent reduction in hospitalization days comparison between MPPT and comparators

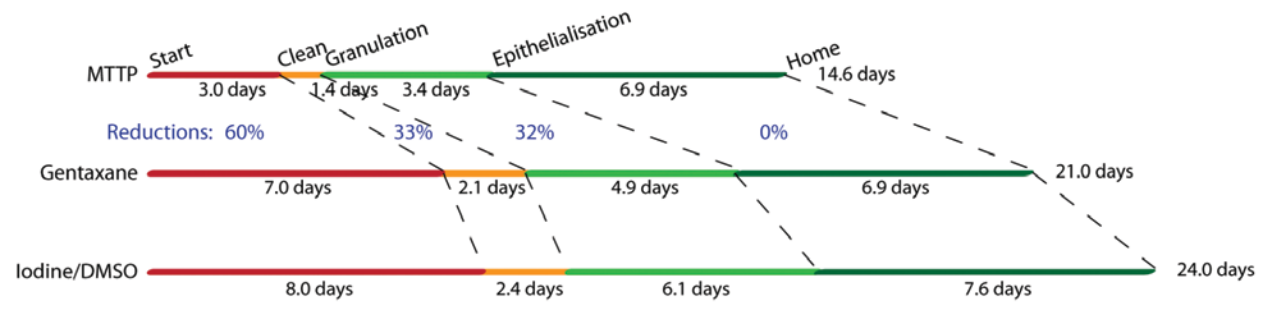
	MPPT vs. Gentaxane	MPPT vs. Iodine/ DMSO	N/group (MPPT, Gentaxane, Iodine/DMSO)
All patients	31%[a]	39%[a]	88, 90, 88
Wounds	41%[a]	44%[a]	30, 30, 30
Venous leg ulcers	19%[b]	36%[a]	20, 18, 16
Diabetic foot ulcers	31%	51%[c]	12, 13, 10

MPPT: micropore particle technology; DMSO: dimethyl sulfoxide
[a] $P<.001$
[b] $P<.05$
[c] $P\leq.01$

eTable 7. Days between wound stages for all study patients

Mean±SD	Days to Clean Wound	Clean Wound to Onset of Granulation	Onset of Granulation to Onset of Epithelialization	Onset of Epithelialization	Onset of Epithelialization to Leaving Hospital
MPPT	3.0±0.9	1.4±0.6	3.4±1.0	7.8±1.1	6.9±5.2
Gentaxane	7.0±1.2	2.1±1.0	4.9±1.5	14.1±1.9	6.9±10.1
Iodine/DMSO	8.0±1.1	2.4±1.1	6.1±2.3	16.4±2.7	7.6±7.4
ANOVA	F(2,263)=546.0; *P*<.001	F(2,263)=23.6; *P*<.001	F(2,263)=58.6; *P*<.001	F(2,263)=441.3; *P*<.001	F(2,262)=0.2; *P*=NS
MPPT vs. Gentaxane	57% reduction *P*<.001	33% reduction *P*<.001	32% reduction *P*<.001	45% reduction *P*<.001	1% reduction *P*=NS
MPPT vs. Iodine/DMSO	62% reduction *P*<.001	39% reduction *P*<.001	45% reduction *P*<.001	53% reduction *P*<.001	9% reduction *P*=NS
Gentaxane vs. Iodine/DMSO	12% reduction *P*<.001	9% reduction *P*=NS	19% reduction *P*<.001	14% reduction *P*<.001	9% reduction *P*=NS

SD: standard deviation; MPPT: micropore particle technology; DMSO: dimethyl sulfoxide; NS: not significant



eFigure 5. Duration of wound healing phases for each of the 3 groups and percent reduction by micropore particle technology (MPPT) compared with Gentaxane and iodine with dimethyl sulfoxide (DMSO).