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Silvetti

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[54] **METHOD OF TREATING WOUNDS WITH A MEDICINAL DRESSING**

[76] Inventor: **Anthony N. Silvetti,** 930 N. Ashland, River Forest, Ill. 60305

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 102,942, Dec. 30, 1970, abandoned, which is a continuation-in-part of Ser. No. 770,414, Oct. 25, 1968, abandoned.

[52] **U.S. Cl.** **424/180,** 424/DIG. 13

[51] **Int. Cl.** **A61k 27/00**

[58] **Field of Search** ..... 424/180, DIG. 13

[56] **References Cited**

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Primary Examiner—Albert T. Meyers
Assistant Examiner—Norman A. Drezin
Attorney, Agent, or Firm—Wolfe, Hubbard, Leydig, Voit & Osann, Ltd.

[57] ABSTRACT

A method for use in the treatment wounds; e.g., second and third degree burns, stasis ulcers, trophic lesions such as decubitus ulcers, severe cuts and abrasions, employing a medicinal dressing containing as an essential ingredient a sterile, purified starch hydrolysate material having a Dextrose Equivalent of less than about 35, and preferably between about 5 to about 25.

5 Claims, No Drawings

METHOD OF TREATING WOUNDS WITH A MEDICINAL DRESSING

RELATED APPLICATIONS

This application is a continuation-in-part of my copending application Ser. No. 102,942 filed on Dec. 30, 1970 now abandoned which was a continuation-in-part of my application Ser. No. 770,414 filed on Oct. 25, 1968, now abandoned.

DESCRIPTION OF THE INVENTION

This invention relates to the treatment of skin wounds; e.g., second and third degree burns, stasis ulcers, trophic lesions such as decubitus ulcers, severe cuts and abrasions, and more particularly to a method for treating burns and exudative lesions with a medicinal dressing.

The aforementioned skin wounds are characterized by open wounds or gaps in the skin tissue. As the healing process progresses these open wounds are gradually filled in by new cells which appear across the surface of the open wound so that when the healing process is complete, new skin tissue covers the former open area of the wound. Such cells are termed granulation cells and the healing mechanism is a granulation cell formation process. These granulation cells are, however, very fragile and rupture easily. Heretofore, conventional dry gauze dressings have been used widely on such burns or exudative lesions. When dry gauze is removed, as for example when it is changed, the cells rupture; thus temporarily arresting the healing process. A dressing for burns and exudative lesions, therefore, should be capable of removal without disturbing the growth of the very fragile granulation cells.

As a defense mechanism the body rushes edemic fluids to the area of these skin wounds and such wounds usually exude this edemic liquid. Consequently, vital body fluids are lost in the exudate. If the loss of such fluids is great enough, shock ensues. Heretofore, the conventional technique to prevent this loss of vital body fluids has been to attempt to seal off the exuding wound. This has been accomplished, for example, by applying to the wound a layer of petrolatum of other water immiscible gelatinous hydrocarbon material. However, it has been found that the tissue under such a layer of petrolatum is often excessively soft and wet. This softened tissue causes difficulty in both autograft and homograft skin transplants. It also provides an environment that is conducive to the growth of secondary infections. The wound, therefore, must be cleansed constantly. But cleansing necessitates removal and replacement of the dressing and, as described above, there is great danger of rupturing the very fragile granulation cells during this removal and replacement process.

Gelatinous protein films have been used instead of a petrolatum seal in the treatment of burns or exudative lesions, but encounter the same problem of the underlying tissues becoming excessively soft. In addition, these films have a tendency to lift up and must then be removed and reapplied. This removal and replacement process again creates the possibility of rupturing the very fragile granulation cells.

A method for the treatment of the aforementioned skin wounds should, therefore, employ a dressing which is as close as functionally possible to a natural

wound scab, be permeable to exudate but not to proteinaceous material, be flexible and not lift up, and inhibit the start or spread of secondary infections by reducing the bacteria count around the treated wound. In the treatment of second and third degree burns, the dressing employed should be similar to a skin autograft in that it affords a natural protective covering which promotes healing, and yet it should, like a homograft, be easily sloughed off by the body when the healing process is completed.

I have now found a new and novel method of treating skin wounds which comprises applying to the wound a sterile, purified starch hydrolysate material having a D.E. of less than about 35. D.E. is an abbreviation for "Dextrose Equivalent," which is an expression in the art for describing the total reducing sugar content of a material calculated as dextrose, and expressed as per cent, dry basis. This value may be measured by any of the methods known in the art such as by the Luff-Schoorl Method (NBS Circular C-440), page 195 as appearing in "Polarimetry, Saccharimetry and the Sugars".. Authors: Frederick J. Bates and Assoc. A low D.E. starch hydrolysate product is one having a D.E. of less than about 35. As heretofore has been mentioned, in practicing the invention I use a sterile, purified starch hydrolysate material having a D.E. of less than about 35, however, the preferred sterile, purified starch hydrolysate materials have a D.E. of between about 5 and about 25. This material is water soluble so that it need not be mechanically removed from a wound; it can be washed away by flooding with water. When applied to an exudative skin wound as a dressing, this material dissolves slightly in the exudate to form a covering which is very similar to a natural wound scab. This covering has been found to be somewhat flexible so that some movement of the treated area is possible without causing the covering to lift up and away from the exudative wound.

The dressing also has been found to act as a semipermeable membrane which allows edemic liquids to pass through it while proteinaceous materials are retained within the body. The exudate is clean and relatively free of proteinaceous materials. It, therefore, does not support biological oxidation to the same extent as exudate containing proteinaceous fluids is minimized while at the same time excessive build up of edemic liquids is also minimized. The possibility of the patient going into shock is, therefore, greatly reduced.

I have also found that when applied to an exudative skin wound, this dressing greatly reduced the bacterial count of an infected wound, and inhibits infection of an uninfected wound. Thus, the possibility of a secondary infection occurring is greatly reduced. Toward this end the sterile, purified starch hydrolysate particulate material having a D.E. less than about 35 may be admixed with any of the antibacterial agents known to the art to be effective in the prevention or treatment of secondary infections, e.g., iodine, penicillin, nitrofuranes and the sulfa drugs such as silver sulfadiazine. In addition, proteolytic enzymes known by the art to be effective in promoting healing may also be admixed with this particulate material. Furthermore, nutritive agents, such as the amino acids, cystine and cysteine, and vitamins, such as ascorbic acid (Vitamin C), may also be admixed or applied along with this particulate material to promote the formation and growth of healthy granulation tissue.

The sterile, purified starch hydrolysate material having a D.E. of less than about 35 can be applied as a particulate material such as a powder, or as a viscous material such as a gel, paste, dispersion, solution or syrup. Such viscous starch hydrolysate can be made by adding the starch hydrolysate to a non-toxic, polar liquid vehicle or carrier such as water, glycerin, glycols or polyols.

The low D.E., sterile, purified starch hydrolysate material may be applied directly to the wound or it may, to facilitate handling and storing, be applied to a bibulous backing, as for example a sterile gauze pad, and the bibulous backing then applied to the wound so that the starch hydrolysate material comes into contact with the skin wound.

As has been previously mentioned, when the low D.E. starch hydrolysate material is applied to an exudative wound a film resembling a natural wound scab is formed. To promote the formation of this protective film, the formation of the protective film, the treated wound should not be tightly bandaged, but should only be loosely covered so that the wound can "breathe." It has been found that application of this material serves also to reduce the pain that is usually associated with burns, ulcers, and the like. This film also has the aforementioned properties of being flexible, semipermeable, soluble in water and antiseptic to the bacteria of the wound.

Starch hydrolysate materials for use in practicing the present invention are those having a D.E. of less than about 35, and preferably from about 5 to about 25. These materials are produced from starch by hydrolysis.

Starch is a polymer of anhydro-D-glucose units. Hydrolysis of starch produces a mixture of polymers of various molecular weights ranging from 200 glucose units or more down to maltose (2 glucose units) and D-glucose itself. Because of their nature the accepted way to describe the polymers formed by hydrolysis of starch is by their D.E. value, which is an expression of the average extent of hydrolysis.

Low D.E. products suitable for use in the present invention may be made by subjecting gelatinized starch to the hydrolytic action of an acid or an enzyme or successive treatments with such agents. The hydrolysate so formed is then purified by conventional means such as by subjecting it to filtration, centrifugation, decantation or the like to separate and remove any water insoluble materials remaining after hydrolysis. This material, dissolved in water to the extent of 10 grams per 100 ml. will contain less than 0.1 percent insoluble material as determined by filtration and drying the residue to constant weight under vacuum at 100° C. If desired the hydrolysate material may be subjected to further purification steps known to the art such as carbon or clay treatment, dialysis, electrodialysis, osmosis, ion exclusion, ion exchange and the like. The starch hydrolysate material employed in practicing the invention may be prepared from starch by a number of specific methods.

In one method a starch, such as waxy starch, is treated with a single enzyme application of bacterial alpha-amylase. More specifically, an aqueous slurry of a starch such as waxy starch having a solids content less than 50 percent is subjected to the hydrolytic action of bacterial alpha-amylase under suitable conditions to produce the starch hydrolysate material. This material is futher specifically characterized as having the sum of the percentages (dry basis) of saccharides therein with a degree of polymerization of 1 to 6, divided by the D.E. to provide a ratio greater than about 2.0. This ratio is referred to as the "characteristic or descriptive ratio." Those materials having a descriptive ratio less than about 2 are somewhat undesirable in that they exhibit less water solubility and also tend to form a haze in solution as compared to those products with a ratio of about 2 or greater.

Suitable starch hydrolysate materials may also be made via a number of other routes. For example, a mixture of starch and water having a solids content less than 50 percent may be first subjected to the hydrolytic action of a bacterial alpha-amylase. After an initial thinning by the enzyme, the resulting partial hydrolysate is heated to a temperature sufficient to solubilize any unsolubilized starch. Since this temperature also tends to inactivate the enzyme, it is then necessary to subject the solubilized partial hydrolysate to a second hydrolysis by treatment with more bacterial alpha-amylase to obtain the final starch hydrolysate.

A third method of making the preferred class of starch hydrolysate materials consists of hydrolyzing a mixture of starch and water by the action of acid to reach a D.E. of less than about 35. The partial hydrolysate is subsequently subjected to the action of bacterial alpha-amylase to obtain a starch hydrolysate having a D.E. between 5 and 25.

A particularly preferred product useful here has the following specifications: moisture content 5 percent maximum; 9–13 D.E.; pH of 4.5 to 5.5 when in aqueous solution at 10 percent solids; an average bulk density of 28–35 pounds per cubic foot and a descriptive ratio of about 2.

Any starch or starch like material may be used to prepare the starch hydrolysate material used in the invention. Suitable materials include cereal and tuber starches, such as corn, wheat, potato, tapioca, rice, sago and grain sorghum, waxy starches may also be used. Hydrolysis may be carried out by enzymes, acids or combinations of the two.

The materials used in practicing the invention should, of course, be sterile. Sterilization may be accomplished by any of the known sterilization procedures.

For the purpose of illustrating the present invention but not of limiting the same there is set forth below examples of the novel method of treatment and medicinal dressings herein described.

EXAMPLE 1

The subject for this example was a 78 year old man afflicted with Buerger's disease, or arteritis obliterans, that was manifested by chronic, foul smelling, seeping deep ulcerations of both legs. The subject was undernourished and previous attempts to treat the ulcers, by several standard methods, had failed. The ulcers were of a third degree depth, and extended along most of the length of the anterior aspect of the legs. The lesions on the right leg were selected for treatment with a sterile, purified starch hydrolysate particulate material. The lesions on the left leg were treated, as a control, with a nitrofurazone impregnated gauze, a widely used treatment for burns and ulcerated lesions. Bacteriological cultures were taken at various intervals from the lesions

of both legs. The treated lesions were inspected every other day.

As soon as the starch hydrolysate material in powdered particulate form was dusted, in a thin film, onto the ulcer bed or granulation tissue of the lesions upon the subject's right leg, it was wetted by the serum exudate present at the ulcer site, and shortly this wetted hydrolysate product dried up and formed a pliable, thin film. Over this newly formed film, a plain gauze dressing was placed. As compared to the lesions treated with the nitrofurazone impregnated gauze, there was a definite decrease in the amount of fluid exuded from the lesions treated with the starch hydrolysate product. In addition, there was a decrease in the odor of the test site, and a decrease in the pain. The color of the exudate formed at the starch hydrolysate treated site was of a light brown, caramel nature, as compared with the control site, which was a dark, ugly greenish-blue.

A few days after the initial application of the starch hydrolysate product, a change in the characteristics of the granulation tissue of the treated lesion was observed. This granulation tissue became progressively cleaner and bright red, beginning to grow, or fill up, towards the surface of the leg. The gauze over the treated site became securely attached to the wound, whereas the gauze over the control remained unattached. The gauze of the treated site could be loosened by washing with water when inspection or changing of the film was desired.

As indicated, the areas were inspected every other day. It was found that the epithelium began to grow in the ulcer that was treated with the starch hydrolysate product, both from the perimeter of the lesion and from the depth of the lesion. After 7 weeks, the test lesion had completely healed, or filled with newly formed epithelium. This new skin was flexible, warm and pink. The control site, however, after this 7 week period, evidenced no decrease of infection or exudation nor any growth of epithelium. In fact, the control treated ulcerated lesion deepened to the point of involving the muscles of the subject's leg, which became necrotic.

Bacterial cultures taken during the course of the treatment became negative in the starch hydrolysate dressing. However, bacterial infection persisted almost unabated in the control or nitrofurazone treated lesion.

EXAMPLE 2

The subject was a 13 year old girl with a third degree burn of the dorsal aspect of the right foot. The burn was thermal in nature, being caused by boiling water. The subject was treated with antibiotics. At the end of 14 days of treatment, separation of the eschar took place, leaving a deep area of granulation tissue. This area was treated, in the conventional manner, with nitrofurazone impregnated gauze. After a period of three weeks of treatment, the condition of the burn site remained unchanged and, in fact, became progressively more infected. At this point, as no growth of epithelium was observed, normally a split thickness skin auto-graft would have been applied in order to effect healing of the burn.

Instead, however, starch hydrolysate material of this invention in a powdered, particulate form was applied, every other day, to the burn site. After the formation of the thin film, as described above in Example 1, the burn site was covered with a layer of dry gauze bandage.

Again, as with Example 1, the following observations were made: there was decrease of pain from the moment of the application of the hydrolysate product; a decrease of the infection at the burn site; an improvement in the quality and appearance of the granulation tissue; and a progressive growth of the epithelium from the periphery towards the center of the burn site. After 5 weeks, the burn site was completely covered by newly formed epithelium, without any appreciable contracture. After 4 months, no contracture of scars were observed in the area of the original burn site.

EXAMPLE 3

The subject, a woman 51 years old, was affected with bilateral deep stasis ulcers of both legs, at the lower third of the leg. The right leg ulcer was rather small, and measured approximately 3 by 4 inches. The ulcer on the left leg, in contrast, covered completely around the leg in a circular fashion, and had a width of 5 inches.

The drainage from both ulcers was considerable, the subject having to use several thicknesses of cotton dressing to control the drainage. The right leg ulcer was used as a control and treated, as in the examples above with nitrofurazone impregnated gauze. The left leg was dusted with the starch hydrolysate material of this invention, in powdered, particulate form every other day. After approximately 2 months, the leg treated with the starch hydrolysate product was almost completely covered by newly formed skin, with the exception of a centrally located area, which continued to decrease in size as new epithelium formed. As in the examples above, the following observations were made: there was a decrease of pain; a decrease of drainage and exudate; growth of granulation tissue; centripetal growth of the skin; and dimunition of the bacterial flora and bacterial count. Again, as in the above examples, the nitrofurazone treated ulcer showed little healing.

EXAMPLE 4

The subject for this example was a 56 year old woman who had had a deep stasis varicose ulcer on her right leg (internal lower aspect) for approximately 20 years. The wound measured 6 inches by 4 inches and was foul smelling with an abundant yellowish-greenish purilent exudate. It was infected with abundant bacterial colonies of at least three species. Previous attempts to autograft and homograft over the area had been unsuccessful. The affected area was treated over several months with various available systemic and topical antibiotics with no change whatsoever in the status of the ulcerated area.

To this ulcerated area sterile, purified starch hydrolysate material in powdered particulate form was applied in an amount sufficient to form a thin layer over the wound. The D.E. of this material was about 9.9. Within a few minutes after application the particulate material mixed with the exudate serum to form a film. If left uncovered, the film would dry up within an hour to form a solid, yet flexible covering over the ulcer site. This covering resembles a natural wound scab, and like a natural wound scab it prevents body fluids (i.e., plasma) from escaping and regulates temperature exchanges from the body through the wound.

Following applications of the particulate material at intervals of 2 or 3 days, it was noticed that the exudate from the wound diminished appreciably so that after fifteen days of such treatment the ulcer site showed no trace of purilent exudate or other debris. After this time the centripidal growth inside the wound site was estimated to be about 2½ inches with the ulcer reduced to 1½ inches × ¾ inch in size. With a magnifying glass the advancing edge of the epidermis could be seen growing into the granulation tissue covering the reduced site of the ulcer. There was no pain associated with the treatment.

EXAMPLE 5

The subject was an 11 year old girl who had suffered first and second degree thermal burns (scalding water) on the left flank of her abdominal wall (her left side above the hip area). The burn site was 7 inches by 4 inches. To this burn area sterile, purified starch hydrolysate material in powdered, particulate form was applied in an amount sufficient to form a thin layer over the burn. The D.E. of this material was about 9.9. On the second post-burn day the superficial layers came off having a second degree burn. After daily treatment with the particulate material for 6 days, the burn area was fully re-epithialized. There was no infection and no pain associated with the treatment.

EXAMPLE 6

The subject was a 5 year old girl who had a second degree thermal burn (hot coffee) on her forearm. The burn was 3 inches by 1 inch and had three small areas of a third degree burn. The burn was treated as in Example 5 with sterile, purified starch hydrolysate material in powdered, particulate form on the third post-burn day. At that time the burn was already infected. The D.E. of the material used was about 9.9. The material was applied every other day. After 10 days the burn area was fully healed and covered by new epithelium including the third burn areas. One month later there was no evidence of scarring.

EXAMPLE 7

In this test 40 young adult New Zealand strain albino rabbits, weighing between 2 and 3 kilograms, were first subjected to a third-degree burn over approximately 10 percent of their total body surface area and then separated into four test groups. Each test group consisted of five males and five females. One group was a control group and the burn site areas of the rabbits in the other three groups were treated with different dosages of a sterilized dispersion of a starch hydrolysate having a D.E. of about 10 and a descriptive ratio of about 2.

In preparation for the test, the back of each rabbit was shaved using electric clippers. This exposure site constituted approximately 10 percent of the total body surface area.

At the end of the 24-hour recovery period, just prior to the first application, each rabbit was burned by immersion of the shaved surface in hot water, using a temperature of 90° C and exposure time of 4 seconds which was determined experimentally appropriate for producing a third-degree burn involving approximately 10 percent of the total body surface area. In order to prevent accidental ingestion of the test material, each rabbit was fitted with a lightweight, flexible, plastic collar which was worn throughout the investigation.

Calculated doses of the test suspension were gently distributed (without rubbing) over the entire application site of each test animal and allowed to contact the skin for a period of 18 hours. At the end of the 18-hour contact period the skin was rinsed with warm sterile water (3° C) and patted dry. This procedure was followed daily including weekends for a total of 21 consecutive days. Doses were re-calculated weekly to adjust for 37° in body weights.

An outline of the test groupings and dosages employed is given in the table below.

Group	Number of Animals Male	Female	Dose Level* (g/kg/day)	Number of Daily Dermal Applications**
Burn Control	5	5	—	—
Test I	5	5	1.0	21
Test II	5	5	2.0	21
Test III	5	5	4.0	21

* The test material was prepared by admixing 70 grams of a starch hydrolysate having a D.E. of about 10 and a descriptive ratio of about 2 with sterile distilled water to make a 70 percent w/v product.

** The test suspension was allowed to contact the skin for a period of 18 hours per day after which the skin was rinsed with warm sterile water and patted dry.

The animals in each of the four groups were weighed weekly and several tests, including blood tests and urine analysis, were performed at the beginning of the study and at the end of the 21 day test period.

Two of the 10 animals in the control group (Group I) died during the investigation. In addition, three of the 10 test animals in Group II (dosed at a level of 1.0 g/kg/day), one of 10 test animals in Group III (dosed at a level of 2.0 g/kg/day) and seven of 10 animals in Group IV (dosed at a level of 4.0 g/kg/day) also died during the investigation. Death was attributed to the stress of the induced burn and/or naturally occurring disease. After the test period all surviving animals were sacrified and subjected to gross and microscopic-pathological studies.

No unusual behavioral reactions were noted in any of the animals in any of the four test Groups. The burned skin of the animals treated with the sterile solution of the low D.E. starch hydrolysate product appeared to heal slightly sooner than that of the control animals, i.e., the scabs of the treated animals were beginning to slough off after 12 to 15 days, while those of the control animals were beginning to slough off after 20 to 22 days.

Adverse effects on body weight were noted among animals in all four of the groups and were more pronounced among animals in Groups II, III and IV. This difference was considered to be due at least in part to the stress placed on the animals during the dosing procedure.

Post-mortem pathological studies of the animals that died during the study revealed hyperemia and inflammation of the lungs and skin findings consistent with those previously described. No significant gross or microscopic pathologic alterations were noted among any of the animals sacrificed at the end of the 21-day test period other than the dermal alterations previously described.

While the foregoing representative embodiments and details have been shown for the purpose of illustration and invention, it will be apparent to those skilled in the art that various changes and modifications may be made therein without departing from the spirit or the scope of the invention. It is intended that all such

changes and modifications will be embraced within this invention, provided they fall within the appended claims.

I claim as my invention:

1. A method of treating skin wounds which comprises dusting thereof with an amount of a dry particulate starch hydrolysate having a Dextrose Equivalent of less than about 35 effective to form a film over said wound.

2. The method of claim **1** wherein the starch hydrolysate has a Dextrose Equivalent between about 5 and about 25.

3. The method of claim **1** wherein the starch hydrolysate has a Dextrose Equivalent between about 9 and about 13.

4. A method of treating skin wounds which comprises applying thereto an amount of a starch hydrolysate having a Dextrose Equivalent of less than about 35 effective to form a film over said wound.

5. The method of claim **4** wherein the starch hydrolysate has a descriptive ratio of about 2 or greater, the descriptive ratio being the quotient obtained by dividing the sum of the percentages of saccharide, dry basis, having a degree of polymerization of 1 to 6 by the dextrose equivalent.

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