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Effectiveness of Honey for Healing Chronic Wounds Compared to Standard Treatments

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Effectiveness of Honey for Healing Chronic Wounds

Compared to Standard Treatments

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INTRODUCTION

As the concern grows for antibacterial-resistant bacteria, traditional methods for wound care are being re-evaluated such as the use of honey. Honey has been used for thousands of years to heal wounds with documentation found as early as Egyptian times in 1550 B.C. [1] It has been found to cause dehydration of bacteria, is bacteriostatic by its acidic nature, produces antioxidants, has an anti-inflammatory effect, and yields the phytochemical factor methylglyoxal (MGO) which has been found to have antibacterial activity.[2]

As referenced in Molan's paper[3], Cooper, Molan, and Harding[4] tested honey's antibacterial properties with results concluding complete inhibition against multiple strains of MRSA (methicillin-resistant *Staphylococcus aureus*), 58 strains of coagulase-positive *Staphylococcus aureus,* and 20 strains of *Pseudomonas* sp. with the use of honey in concentrations ranging from 1.8-11% volume.

Honey is glucose-based, and this property allows the sugar molecules to bind with water molecules, increasing the bacterial osmolality and effectively desiccating bacteria.[3] Excessive wound exudate will reduce honey's osmolality but it is still completely inhibitory up to exponentials of between seven- to fourteen-fold.[4] Despite this, its other antibacterial properties are still able to sustain wound sterility in as little as three days.[5] An enzyme that bees add to nectar creates hydrogen peroxide, which is largely the thought attributing to honey's antibacterial properties.[3] In the body being able to utilize this enzyme, medical honey is defined as an autolytic debridement agent compared to other autolytic or enzymatic agents currently on the market. While hydrogen peroxide can be damaging to bacteria, it can also be damaging to wound tissues; however, honey has high levels of antioxidants which act as a protectant for wound tissues by

reducing the oxygen radicals.[3] This goes in turn with honey having anti-inflammatory properties which are often caused by oxygen radicals.[3]

Due to bacterial-forming organic compounds of ammonia, sulphur, and amines, wounds commonly have malodor.[3] Another property of honey is its odor-reducing ability due to bacteria utilizing the glucose present instead of amino acids, resulting in lactic acid production instead of the aforementioned compounds.[6]

Stimulation of healthy granulation tissue has been evident with honey.[5] This is multifactorial including the byproduct of hydrogen peroxide which, in low volumes, stimulates angiogenesis,[3,7] increased oxygenation of the wound by honey's acidic nature with its pH of 3-4,[3,8] increased circulation due to its ability to reduce wound tissues' hydrostatic pressure,[3,9] and the large nutrient component of honey. Trace elements, amino acids, and vitamins are commonly found in honey.[3,10] This combined with its high osmolarity causes a fluid shift of lymph into the wound, providing nutrients for generation of healthy tissue.

However, with many advances in wound care including a copious array of new products, the authors are curious if honey as an age-old treatment is still competitive in its effectiveness for healing wounds.

Nature of the Problem

Chronic wounds develop with sequelae such as diabetes (neuropathy, muscular atrophy, change in gait resulting in change in applied pressure, poor glucose control leads to wounds and decreases wound healing), pressure, peripheral arterial disease (hypoxia), peripheral vascular disease, trauma causing destruction of tissue that may not heal without intervention, and malnutrition.

The normal phases of wound healing are hemostasis, inflammation, proliferation, and tissue remodeling. When there is interruption of the natural progression of these phases, chronic wounds ensue. It is unclear of the exact time frame between an acute and chronic wound, but experts would agree it is typically between 4-12 weeks. Oftentimes, chronic wounds become stationary in either the inflammatory phase or proliferative phase, stalling wound healing.[11] Therefore, an alteration in the wound bed such as decreasing hydrostatic pressure, increasing circulation, changing osmolality, decreasing bioburden, or sharp debridement can all aid in putting the wound back into the normal phases of wound healing.

Diabetes is a major contributor for chronic wounds. *Podiatry Today*[12] cites that 15% of diabetic patients of the 16 million diabetic Americans will develop foot ulcers. A newer study in 2017[13,14] with the same journal cited the American Diabetes Association's 29.1 million Americans having diabetes and 25% of diabetic patients will develop a foot ulcer. This latter statistic, while newer, is likely a low estimate given the ADA's recent number and the Singh study data being from 2005.[14] Diabetic care is evaluated with the blood test Hemoglobin A1c (HgA1c) which measures the average blood glucose in the past 2-3 months. In a retrospective cohort study with n=183 in 2011,[15] with each point of HgA1C above 8%, wound healing decreased by 0.028cm^2 daily (p=0.027).

Pressure ulcer incidences vary widely from 0.4-38% in acute care settings, 0-17% in home care, and 22-23.9% in long-term care facilities.[16] Gupta et al.[17] described pressure ulcers as long-term wounds as the normal healing phases are interrupted due to oftentimes both local and systemic factors. These include continued pressure which leads to soft tissue, subcutaneous fat, and muscle damage caused by ischemia and even necrosis of the tissue being compressed, edema, moisture, localized infection, systemic infection, renal and hepatic insufficiency or failure,

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anemia, mediocre to poor nutritional status, diabetes, and circulatory dysfunction. Frequently, alleviating the pressure-inducing agent will, in time, heal the pressure wound if it is mild; but, with associated factors, this is not always as straightforward as it seems.

Hypoxia occurs due to decreased oxygen availability. It is often seen with peripheral arterial disease (PAD: narrowing of the arteries decreases blood flow, leading to decreased oxygen). This is due to arterial cholesterol deposits (atherosclerosis), hardening of the arteries (arteriosclerosis; commonly seen with smokers), or both and it frequently occurs in conjunction with coronary artery disease (CAD). Wounds need oxygen to heal by releasing growth factors to induce angiogenesis; but with hypoxia, cytokines and a surplus of reactive oxygen species are produced, causing tissue damage.[18] Tips of toes, lateral malleolus, proximal lower leg, and distal foot are common arterial wounds sites with round, well-defined borders, and minimal drainage; they are also typically painful. PAD can be controlled somewhat by cholesterol-lowering medications, reducing sodium and alcohol intake, and quitting smoking; age is also a factor as, with high ages, the damage may not easily be stabilized or reversed.[19] In situations of PAD of moderate to severe disease, revascularization by angioplasty, stenting, or bypass is performed, provided the patient is a good surgical candidate.

PAD is an organic type of Peripheral Vascular Disease (PVD). PVD is most often due to chronic venous insufficiency with venous ulcers developing due to poorly functioning valves causing congestion of blood in the legs. Essentially, blood can get to the wound but then has a difficult time getting back to the heart as the vein valves may spasm or work poorly. Positive family history, nicotine use, diabetes, dyslipidemia, hypertension, sedentary lifestyle, and obesity can all contribute to developing PVD. Medial malleolus and medial lower leg are common venous ulcer sites. Venous ulcers typically have irregular borders and are commonly associated

with dark erythematous-violaceous distal legs and bilateral lower leg edema ("pitting" or "weeping" edema is common due to third-spacing of fluid out of the venous system and into the localized tissues) or lymphedema. Treatment includes compression (dry or wicking bandages, pneumatic pressure devices), elevating legs, vein stripping, or sclerotherapy.[20]

Malnutrition is a huge component of poor wound healing. Trujillo suggested influential factors of chronic wounds include both protein and energy malnutrition.[21] Vitamin A encourages epithelialization, Vitamin C aids in collagen formation, and zinc aids in cellular proliferation. Protein is needed for development and maintenance of amino acid chains, collagen, keratin, and muscle fiber proteins actin and myosin.[22]

At multiple nursing facilities, when a patient develops a wound, s/he is automatically started on a protein supplement, Vitamin C, Zinc, and a multivitamin. Protein demands can increase up to 250% with caloric needs increasing 50%.[23, 24] Based on the recommendations by National Pressure Ulcer Advisory Panel (NPUAP), intake should include calories of 30-35 kcal/kg, protein 1.25-1.5 g/kg (minimum is 0.8 g/kg), and fluid intake of 1 mL/kcal/day).[25]

Review of the Literature.

The Cochrane review by Jull et al.[26] had a large trial size, double-blind studies, and multiple trials researched. Researchers had a large RCT of 3,011 participants yielding a mix of high quality with lesser quality results. In two trials totaling 992 participants, honey produced better results over conventional dressings for healing partial thickness burns more quickly (WMD -4.68 days, 95% CI -5.09 to -4.28) but the evidence was inconclusive regarding potential infection or adverse reactions. It was also noted with only moderate quality evidence that honey was more effective in quickly healing post-operative infections compared to antiseptic washes.

Unfortunately, there was also low quality data produced regarding better healing via early excision and grafting of burns (both partial and full thickness) compared to honey, healing of acute and chronic wounds more quickly by honey compared to silver sulfadiazine (SSD) or sugar dressings, or even honey healing Fournier's gangrene better compared to Eusol soaks. Additional low-quality evidence was admitted regarding honey versus competitors' products for healing venous leg ulcers and diabetic foot ulcers. In conclusion, honey was only superior to alternative current treatments in healing partial thickness burns faster and post-surgical wound infections.[26]

In a research study done by Biglari et al.[27] with *n*=101 covering hospital patients varying from child to adult and including oncology patients, wound volumes decreased with use of honey dressings between 39.4-100% on average (± 47.14) and 31.7% of the wounds healed in the approximate five-week study (± 3.83), both with clinical significance (p-value <0.05). The authors noted that one-third of the patients had an underlying malignancy which can certainly contribute to wounds not healing compared to healthy, immunocompetent patients. It was also noted that honey reduced pain, necrotic tissue, and slough for the wounds.

Efem[9] performed a study of individuals who failed conventional treatments (Eusol solution; dressings with acriflavine, Sofra-Tulle or Cicatrin; topical and systemic antibiotics) for wounds of time span one month to two years. With a 98.3% success rate of *n*=59, honey was found to be an effective product with maintaining sterility of the wounds, reduction in periwound edema, fast epithelialization, and debridement by replacing necrotic tissue with granulation tissue. The author noted that the one failed-treatment patient of the study had a Buruli ulcer (an extremely rare necrotizing disease of the skin) for which honey was ineffective.

In a 2015 RCT[28] of 715 participants, honey was reported to have healed 44% of venous leg ulcers compared to 33% over hydrogel (an autolytic debridement agent) in a 12-week span. A

second trial was later performed and found that honey also had a superior reduction in wound size compared to hydrogel (p-value <0.001). However, the authors concluded that, due to lack of meta-analysis and the low number of studies (10), they are unable to confidently state that honey had any benefit.

PluroGel is a micelle surfactant wound gel that works by keeping the wound moist but also absorbing exudate and necrotic tissue within the gel.[29] Podiatrist Dr. Landsman has described PluroGel as a powerful surfactant as it can absorb several fold its weight in necrotic tissue or debris while maintaining a moist environment.[30]

Saeed[31] led a small double-blind RCT comparing manuka honey-impregnated gauze versus tulle grass and absorbent dressing for diabetic foot ulcer patients. The study (*n*=57) showed a clinically significant decrease in toe amputations (9.7% vs 34.6%), faster healing time at both the 6-week and 6-month intervals, and hospital stay with resolution of infection.

Alginate dressings are derived from seaweed and have an ability of absorbing up to 20 times their own volume of wound drainage due to their hydrophilic properties.[32] In absorbing drainage, the seawood also keeps the wound bed moist and contributes to enzymatic debridement. Silver has been added to alginate dressings for wounds with high bioburden or a large amount of exudate with success over their alginate partners that do not contain silver.[33,34]

A prospective RCT (*n*=36) comparing silver alginate with calcium alginate showed at four weeks' time, there was a reduction of risk for infection by reducing bioburden as well as progressing the wounds' ability to heal for both dressings, but clinically significantly more so for the silver alginate dressing.[35]

Study Objective

To determine if a homeopathic, natural, relatively accessible, and affordable product such as medical honey can be used with comparable efficacy against current products for chronic wounds.

METHODOLOGY

Materials

- Patient population: Adult population. Will also compare subgroups of ages 20-39, 40-59, 60-75, 76-89
- Intervention: medical-grade honey
- Compared against: standard treatments: honey with calcium alginate, hydrogel, PluroGel.
- Outcome: at least comparable in healing chronic wounds
- Retrospective chart review

Manuka honey is the product to be tested as it is highly available. It is found most often labeled as Medihoney ®. DermaSciences produces Medihoney ® which has been sterilized by gamma irridiation. This also destroys *Clostridium botulinim* spores which is most often seen with children under one year of age ingesting honey.[36]

Facility availability of the products varied but most facilities used regular Medihoney apinate dressings which is antibacterial Medical manuka honey that contains 100% manuka honey and active *Leptospermum* combined with an alginate[37] compared to Medihoney gel which is an antibacterial wound gel of which 80% of the product contains 100% manuka honey; the remaining 20% contains “natural plant waxes.”[38]

Inclusion criteria: adults between ages of 25-89 years with chronic wounds (wounds present for at least 3 weeks).

Exclusion criteria: patients without consistent weekly visits (those who refuse frequently in which wounds cannot be assessed regularly); persons with overall poor health defined as hospice, mortality prognosis of <12 months, active cancer, persons 90 years of age and above.

Data Obtained

Past Medical History: peripheral arterial/vascular disease, recent surgery, immobility, anemia, diabetes, chronic kidney disease, obesity, malnutrition as diagnosed by history or blood work, smoker, dementia or CVA

Blood work: recent HbA1C, nutrition levels as measured by recent albumin, total protein, and/or pre-albumin level, hemoglobin to assess anemia

Patient number: 20 patients for each experimental group

Wound Data collected: use of treatment for at least 3 consecutive weeks (at least 2 dressing changes in a 7-day period), volume measurements, and change of percentage of necrotic tissue present, and amount of drainage (quantified by mild, moderate, excessive) will be obtained for comparison. This data is vital in comparing equivocal wounds with use of various products. Comorbidities will be attempted to be kept consistent within each comparison group. Documentation of sharp debridement also has influence on the wound volume and will be recorded.

Statistical Analysis

Assumptions. It is assumed by the author that all providers documented to the best of their abilities and with utmost honesty in their measurements and clinical evaluations.

Patients were analyzed by their different wound treatment categories. Charts were examined in detail and extrinsic factors such as hospitalization or noncompliance were noted if causing wound deterioration at no fault of the wound treatment itself. Improvements or deteriorations were calculated by percentages with an average weekly improvement or deterioration rate.

Statistical analysis was performed by calculating each treatment's mean, standard deviation, p value, and confidence interval and determining if the null hypothesis that each treatment can successfully heal chronic wounds (a test mean of 1) was supported with scientifically significant results based on the p value.

Commercial bias

Name-brand products such as Medihoney (Integra ®) and PluroGel (Medline ®) were utilized in this research study. No kickbacks or reimbursements were offered or obtained in utilizing the products for this research paper.

Institutional Board Review

As deemed by the University, IRB approval was not required for this retrospective chart review.

RESULTS

In comparing medical-grade honey, honey with calcium alginate, PluroGel, and hydrogel, hydrogel had the most improvement on a weekly basis at 16.53 percent mean with 95.24 percent of patients showing improvement (Table 1). The other products also showed overall improvement but to a lesser degree: medical honey 2.29 percent mean weekly change, medical honey with calcium alginate 13.21 percent mean weekly change, and PluroGel 5.15 percent mean weekly change. It was also noted that wounds treated with hydrogel had the most sharp debridements performed (14) and the most patients with malnutrition (7).

These results are further supported by the p values of each treatment (Table 2). Specifically that hydrogel had the most statistically significant results with a small p value of 0.0015 while medihoney did not show statistically significant results in healing chronic wounds with its p value of 0.0658.

DISCUSSION

Limitations. Limitations of the research data include:

An obvious limitation of the study was the limited number of patient charts evaluated. PluroGel has only been approved by the Food and Drug Administration (FDA) since 2014.[39] Research for this chart review was reflective from 2008 to 2016 to avoid incomplete charts or the need to acquire consent from patients who are still active on the census (many wound care patients have dementia and obtaining consent from their medical power of attorney has previously proven challenging).

Data collection was inconsistent among multiple providers with different levels of documentation thoroughness and follow-through with contributing laboratory values such as

albumin, total protein, and HbA1C as well as a thorough history and physical or documented studies.

Based on the author's and company's own previous use of the product, medical honey has not typically been applied to wounds with quantified moderate or greater drainage.

With newer wound care practice changes and facility documentation requirement changes, after three weeks of a treatment not improving the wound, the product is changed to another product; hence, the limitation of at least 3 weeks' application time. However, as noted in Table 1, older patient charts allowed for longer treatment length.

Implications for Practice

Ultimately, the greatest anticipated benefit is healing the patient's wound(s) in the fastest amount of time with the least amount of pain and the most cost-effective product. In performing this research, multiple products can be compared to determine efficacy of one compared to another for patients with similar presentations and medical histories.

There are numerous articles expressing concern over the rise in health care costs. If hydrogel is the more viable chronic wound healing option compared to current modules of care, this could be a large cost-saver for the patient as well as wound care as a subspecialty.

By having a solid source of evidence to choose a wound care treatment, patients may require fewer wound care visits, they may have less pain as the wounds heal, perhaps fewer sharp debridements may need to be performed, and the goal of healing the wound is achieved more quickly in choosing a product that data has backed and proven to be more effective than another product. Sometimes choosing a more expensive product that is known to work quicker is ultimately cheaper than using a less effective product for longer. This benefits the patient as well as the insurance company or facility that is paying for the product(s) used.

CONCLUSIONS

A larger data pool is needed to further assess the efficacy of products in treating chronic wounds. Given the initial results of hydrogel being superior in treating chronic wounds to medical-grade honey, honey with calcium alginate, and PluroGel, additional studies should be performed. More data will also be collected and studied to better assess product efficacy. These include supplemental medications: (multivitamin, zinc, Vitamin C), patient compliancy, surgical history of percutaneous endoscopic gastric (PEG) or gastric tube to assess malnutrition, and history of osteomyelitis (specifically for current wound areas).

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Appendix A

Table 1.

Chronic Wound Treatments Comparison[40]

Data	**Medihoney**	**Medihoney + Calcium Alginate**	**PluroGel**	**Hydrogel**
Wounds	21	14	15	21
Patients	15	11	13	18
Number of deteriorated wounds	4	1	1	1
Patients showing improvement	80.95%	92.86%	93.33%	**95.24%**
Mean percent change weekly	2.29%	13.21%	5.15%	**16.53%**
Mean percent improvement weekly (excludes wounds with deterioration)	13.50%	14.27%	11.47%	**17.43%**
Average number of weeks of treatment before resolution or treatment change	6.714	6.857	6.733	6.857
Number of wounds sharp debrided (scalpel or curette)	9	11	11	**14**
Mean age	68.0	63.7	70.8	77.0
PAD/PVD (no. patients)	**4**	3	1	3
Diabetes Mellitus (no. patients)	5	3	6	**9**
Pressure wounds (no. patients)	**14**	11	12	**14**
Malnutrition (no. patients)	3	1	5	**7**
Impaired mobility (no. patients)	**13**	12	7	11

Appendix B

Table 2.

Chronic Wound Treatments Statistical Significance Comparison

Values	**Medihoney**	**Medihoney + Calcium Alginate**	**PluroGel**	**Hydrogel**
Wounds	21	14	15	21
Mean	0.117	0.725	**0.456**	0.738
Standard Deviation	2.079	**0.3086**	0.8742	0.3266
P value	0.0658	0.0054	0.0302	**0.0015**
95% confidence interval	-0.08293 to 1.0633	0.5468 to 0.9032	0.0280 to 0.9400	0.5894 to 0.8866

Appendix C

Target Journal Author Guidelines for Advances in Skin & Wound Care

Scientific Articles for *Advances in Skin and Wound Care*

Purpose: To create original data and translate new findings into practice for improved patient care.

A scientific article is a primary source that presents new data for clinical practice by skin and wound care professionals. We welcome submissions in this category of qualitative, quantitative, or mixed-method studies, including randomized controlled trials, cohort studies, and so on. Although original investigations are the most common type of article we publish, this category may also include case studies or series and literature reviews. We recommend that authors pursue advice from a statistician before publication to avoid any potential methodological issues.

Length of articles: 6000 words or fewer

References: limit these to no more than 50 key recent references

Art: We encourage the inclusion of figures and tables to illustrate your research. The number of art items should be roughly proportional to the length of your paper and depends on the size of the tables, graphs, or photographs. Permission must be obtained by the author and provided to the publisher for any items not created specifically for the article.

Key sections:

- **Title Page:** Include the article title, the full name of each author, his or her credentials including highest academic degree, and current affiliation, including city and state. The title page must also disclose conflicts of interest and funding received for this work from

any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).

- **Abstract:** A structured abstract of no more than 250 words included within the body of the manuscript should contain the following headings: Objective, Design, Setting, Patients (or Participants), Interventions (if any), Main Outcome Measure(s), Main Results, Conclusions, and Keywords.
- **Text:** Include an introduction (with a short literature review and statement of problem), methods, results, discussion (include implications for clinical practice), and conclusions.
    - Introduction/Background
        - Literature Review
        - Study Objective
    - Methods
        - Materials
        - Statistical Analysis
        - Study approval/institutional review
    - Results
    - Discussion
        - Limitations
        - Implications for Practice
    - Conclusions
- **References:** Authors must use AMA (American Medical Association) style for references. Do not use endnotes in the text. Type the references double spaced, numbering each one consecutively the first time it is cited in the text (do not use the author's name in the text;

references must be numbered). Use superscript numbers, placed after the punctuation. List all authors when there are 6 or fewer; for 7 or more, list the first 3 followed by "et al." Authors are responsible for the accuracy of all relevant citations.

- **Book title:** Author(s) (last name and initials, no periods), title (uppercase and lowercase, no quotation marks), edition or volume, city and state/province of publication, publisher, and year. When particular pages are relevant or when the text is referenced several times, list the relevant pages. Example: Lemeshow S, Hosmer DW, Klar J, Lwanga SK. Adequacy of Sample Size in Health Studies. Chichester, England: John Wiley & Sons Ltd., 1990.
- **Chapter in a book:** Follow the directions for book title, but add chapter title and editors. Example: Brandeis G, Powell J, Bergstrom M. Resident assessment protocol: pressure ulcers. In: Morris JN, Hawes C, Murphey K, et al, eds. Resident Assessment Instrument Training and Resource Guide. Natick, MA: Eliot Press; 1991.
- **Journal articles:** Author(s) (last name and initials, no periods), title of article (lowercase, no quotation marks), abbreviation of the journal as given in the Cumulative Index Medicus, year of publication, volume number, and inclusive pages. Example: Allman RM, Laprade CA, Noel LB, et al. Pressure sores among hospitalized patients. Ann Intern Med 1986;105:337-42.
- **Publication by an organization:** Follow example format; include a hyperlink and last accessed date when applicable. Example: National Pressure Ulcer Advisory Panel: Statement on Pressure Ulcer Prevention. Buffalo: NPUAP, 1992.

- **Tables:** Put each table on a separate page after the reference list, double spaced; include a title for each one. Number the tables in the order in which they are referred to in the text. Use the Publication Manual of the American Psychological Association, 4th ed. (1994), as a source for the correct format of statistical tests and tables. Also, if using previously published material, authors are responsible for obtaining written permission from the publisher before submitting the material.
- **Figures:** Submit high-resolution electronic files in .tif, .png, or .jpg format; include a title for each one. Number the figures in the order in which they are referred to in the text. Written permission from the patients must accompany the photographs. Model release forms can be supplied if needed. Also, if using previously published material, authors are responsible for obtaining written permission from the publisher before submitting the material.[41]

Note for reviewers of scientific articles:

These articles are intended to further our shared discipline and present new findings to wound care professionals. The article is best if it builds on previous findings with unique and innovative results and presents the data in a format that can be translated for practice. The emphasis is on presenting new material, and should incorporate expert opinion/experience and patient preference along with healthcare systems considerations such as feasibility and cost.[42]