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## A comparison of topical honey and phenytoin in the treatment of chronic leg ulcers

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### Summary

In view of the reports that phenytoin and honey are useful in the healing of wounds, a comparison of their topical use in the treatment of chronic leg ulcers was carried out. Fifty cases of chronic leg ulceration were studied, each for a period of four weeks. They were assigned into three groups for honey, phenytoin/honey mixture, and phenytoin topical treatment. Overall mean duration of the ulcers was 56.5 months while the mean (s.d.) size was 3339 (5193) mm<sup>2</sup>. Mean percent reduction in size in the group treated with honey, 27.0 (36.9), was not significantly different ( $H=0.26$ ; 2 df;  $p=0.88$ ) from that of the mixture group, which was 25.9 (46.4), and from that of the phenytoin group which was 35.5 (53.2). This percent reduction in size was significantly greater, ( $H=7.69$ ; 2df;  $P=0.02$ ), during the first week in the phenytoin group than in the other groups. Four of the cases progressed to complete healing at the end of four weeks with phenytoin. Pain score difference (using a graduation scale from 0 to 10) at the end of the four week treatment, was, 1.8 (1.7) in honey group, 2.0 (1.3) in mixture group and 3.6 (2.4) in phenytoin group. This difference was not significant, ( $H=3.09$ ; 2df;  $P=0.21$ ). Our study suggests that phenytoin may be superior to honey as a topical agent in the treatment of chronic ulcers.

**Keywords:** Phenytoin, honey, ulcer

### Résumé

Par rapport à des reports selon lesquelles la phénytoïne et le miel sont utiles dans la guérison des blessures, une comparaison de leur utilisation a été faite. Cinquante cas des ulcères chroniques des pieds avaient été étudiés chacun pour une période de 4 semaines. Ils avaient été répartis en 3 groupes traités avec du miel, la phénytoïne/mélange avec du miel, et le traitement de surface avec de la phénytoïne. La durée moyenne totale des ulcères était de 3339 (5193) mm<sup>2</sup>. La moyenne de pourcentage de réduction en taille dans le groupe traité avec du miel était de 27.0 (36.9) et n'était pas différente significativement ( $H=0.26$  df = 2:  $P=0.88$ ) de ceux des groupes traités avec le mélange, qui avait une réduction de 25.9 (46.4). De même il n'y avait pas de différence entre les réductions des ulcères des patients appartenant aux groupes traités à miel et ceux traités à la phénytoïne qui avait pour valeur 35.5 (53.2). Le pourcentage de réduction en taille était significativement élevé ( $H=7.69$ ; df = 2:  $P=0.02$ ) pendant la première semaine de traitement dans le groupe à traitement à la phénytoïne comparé aux autres groupes. Quatre des cas avaient progressé à une guérison totale à la fin des 4 semaines avec la phénytoïne le score des différences en douleurs (en utilisant une échelle de graduation de 0 à 10) à la fin des 4

semaines de traitement était de 1.8 (1.7) dans le groupe traité avec du miel, 2.0 (1.3) dans le groupe traité avec du miel/phenytoin. La différence n'avait pas été significative ( $H=3.09$ ; df = 2,  $P=0.21$ ). Notre étude suggère que la phénytoïne pourrait être supérieure au miel comme agent de traitement de surface des ulcères chroniques.

### Introduction

Chronic leg ulcers and their complications constitute about twenty percent of cases that present to plastic surgery in Ibadan. They commonly affect functional ability, compromise appearance and may be life threatening. Many ointments, powders, gels, sprays, irrigating fluids and dressings are promoted for application to such ulcers. Some though expensive, are claimed to speed healing to justify their cost.

Phenytoin (5.5, diphenylhydantoin) was first introduced into the market as an anticonvulsant. Its healing property was first reported by Bodkin [1] in 1945 after a study of pruritus ani. Honey on the other hand, has been reported to accelerate granulation tissue formation and epithelialisation [2].

In view of reports that phenytoin and honey are useful in the healing of wounds, a comparison of their use in the treatment of chronic leg ulcers is overdue and constitutes the basis of this study.

### Method

Fifty cases of chronic leg ulceration, i.e., leg ulcers of duration greater than six weeks, were studied. The patients, who were attendants of the Plastic Surgery Outpatient Clinic of the University College Hospital, Ibadan, Nigeria were entered consecutively between February and May 1995 and January and August 1996, into honey, phenytoin / honey mixture or phenytoin group. All the ulcers were either posttraumatic or post infective. Known diabetics, patients with sickle cell anaemia and those with venous disease and malignancies were excluded.

The clinical status of the ulcers was assessed by allocation of points, in order to standardize and make each evaluation as objective as possible. The points were allotted as follows:

0. Ulcer healed.
1. Ulcer very healthy, will heal with conservative management.
2. Ulcer with healthy granulation, ready for skin grafting.
3. Slightly uneven or slightly unhealthy granulation.
4. Predominantly granulation but with small area of slough.
5. Moderately sloughy, but interspersed with some granulation



6. very sloughy and very little granulation seen at the surface.
7. very sloughy and discharging moderately
8. dirty ulcer (slough all over) but no local or systemic spread.
9. Dirty ulcer with local or systemic spread.

The surface area of the ulcer was calculated by using double layered tracing paper. While a layer was applied to the ulcer, the second layer, placed on the first was used to trace the outline of the ulcer. The size was then obtained by placing this tracing on graph sheet whose small squares measured 1 mm<sup>2</sup>.

Readings were obtained at recruitment or commencement of dressings and at weekly intervals for four weeks. After each evaluation, the ulcer was cleansed with normal saline and dressed using either topical honey phenytoin/honey mixture or phenytoin as appropriate. Dressings were carried out alternate daily. The phenytoin was applied as a paste consisting of 200 mg of the powder per ml. of normal saline; 1 ml of paste being applied to an ulcer of size approximately 10,000 mm<sup>2</sup>. Honey was obtained from the institution's pharmacy and was applied unprocessed and undiluted. The mixture of phenytoin and honey was obtained as 200 mg of phenytoin powder per ml. of honey; 1 ml. of paste being applied to an ulcer of size approximately 10,000 mm<sup>2</sup>. Over the topical medication, was placed softatulle, then gauze and cotton wool, wrapped over with crepe bandage. The assessor was blinded to the topical medication. Pain at site of ulcer was assessed when the patient attended for dressing, using a graduation scale from which the patient chose a point that reasonably corresponded with his/her level of pain at the time of recording. Minimum pain was graded as 1 while maximum pain was graded as 10.

#### Results analysed included:

1. Mean daily rate of reduction of size of ulcer.
2. Percent reduction in size of ulcer from the commencement of dressings to the end of each week.
3. Change in clinical score from the commencement of dressings to the end of each week.
4. Pain score difference at the end of the four week treatment.

Results were computed as mean (s.d.). Comparison of result was preformed by EPINFO, a software for epidemiology and disease surveillance, using the Kruskal-Wallis one way analysis of variance for nonparametric data. Level of significance was taken to be  $P < 0.05$ .

#### Result

There were 50 chronic ulcer analyses from 38 patients. Thirteen of these were females. Patients' age ranged from 8 to 95 years. Overall mean age was 44.2(20.9) years. Mean age of those in the honey group was 39.6 (23.1) years, for phenytoin/honey mixture, it was 41.1 (18.6) years, while for phenytoin group, it was 50.9 (18.2) years. The difference was not significant (Kruskal Wallis H, equivalent to chi squared, = 3.40; 2df;  $P = 0.18$ ).

The ulcers were situated in the distal half of the leg, ankle, or dorsum of foot, 28 being on the left and 22 on the

right. Duration of ulcer ranged from 1.5 to 324 months. Overall mean duration was 36.5 months. Mean duration in months of honey treated ulcers was 29.1 (60.5) of those treated with mixture, 11.2 (18.1) and of phenytoin group, 108.2 (131.2). The difference between the mean duration of the three groups was not significant ( $H=2.75$ ; 2df;  $P = 0.25$ ). while the smallest ulcer was 166 mm<sup>2</sup>, the largest was 26,226 mm<sup>2</sup> in size. Overall median size was 126mm<sup>2</sup>. In honey group, median size (25%ile) was 1473 (342) mm<sup>2</sup>; in mixture group, 2417 (1145) mm<sup>2</sup>; and in phenytoin group, 1204 (232) mm<sup>2</sup>. The overall mean size of the ulcers was 3339(5193) mm<sup>2</sup>. Mean size of the honey group was 4204 (6795) mm<sup>2</sup>. of the mixture group, 4387 (5669) mm<sup>2</sup>, and of the phenytoin group, 1867 (1893) mm<sup>2</sup>. The difference was not significant ( $H=1.66$ ; 2df;  $P = 0.61$ ).

The average healing rate as measured by rate of reduction in size of the ulcers, Table 1, was fastest during the first week in honey group, fourth week in mixture group, and first week in phenytoin group. A significant difference in healing rate was recorded only during the fourth week ( $H = 6.64$ ; 2 df;  $P = 0.04$ ).

**Table 1:** Daily rate of reduction (healing) of chronic leg ulcers treated with honey, phenytoin/honey mixture, and phenytoin.

Period	Mean rate of healing (mm <sup>2</sup> /day)			KruskalWallis H	p value
	honey	mixture	phenytoin		
1 <sup>st</sup> week	48.3(128.6)	67.6(171.9)	31.4 (45.7)	1.46	0.48
2 <sup>nd</sup> week	11.9 (154.4)	22.1(80.2)	14.3 (80.9)	0.36	0.84
3 <sup>rd</sup> week	27.2(88.8)	10.7 (110.0)	23.6(45.3)	0.01	1.00
4 <sup>th</sup> week	45.1 (80.1)	85.7(101.3)	-19.4(45.0)	6.64	0.04

\* Significant value

Mean percent reduction in size of ulcers in the honey group, 27.0 (36.9), was not significantly different ( $H = 0.26$ ; 2df;  $P = 0.88$ ) from that of the mixture group, which was 25.9 (46.4), and from that of the phenytoin group which was 35.5 (53.2) (table 2). This percent reduction in size was significantly greater,  $H=7.69$ ; 2df;  $P = 0.02$ , during the first week in the phenytoin group than in the other groups. The negative value obtained in the mixture group during the second week reflects percent increase in size. Four of the cases progressed to complete healing at the end of four weeks with phenytoin.

**Table 2:** Percent reduction in size of chronic leg ulcers treated with honey, phenytoin/honey mixture, and phenytoin.

Period: Commencement to the end of	Mean Percent Reduction			KruskalWallis H	p value
	honey	mixture	phenytoin		
1 <sup>st</sup> week	0(14.3)	10.5(16.4)	25.4(24.3)	7.69	0.02*
2 <sup>nd</sup> week	0(23.8)	-10(32.0)	21.7(31.9)	2.38	0.30
3 <sup>rd</sup> week	15.6(28.9)	36.8(22.2)	46.5(41.6)	3.51	0.17
4 <sup>th</sup> week	27(36.9)	25.9(46.4)	35.5(53.2)	0.26	0.88

\* Significant value

Change in clinical scores were not significantly different between the three groups, see tables 3. Table 4 shows number of ulcers that either healed or were ready for skin grafting at the end of four weeks.



Pain score difference at the end of the four weeks treatment, was 1.8 (1.7) in honey group, 2.0 (1.3) in mixture group and was not significant, ( $H = 3.09$ ; 2df,  $P = 0.21$ ).

**Table 3:** Change in clinical score of chronic leg ulcer treatment with honey, phenytoin/honey mixture and phenytoin

Period commencement to the end of:	Clinical Score			Kruskal Wallis H p value	
	honey	mixture	phenytoin		
1 <sup>st</sup> week	1.2(1.4)	0.2(0.6)	0.5(0.9)	4.80	0.09
2 <sup>nd</sup> week	1.5(1.8)	0.8(0.4)	0.9(1.1)	0.38	0.83
3 <sup>rd</sup> week	1.0(1.6)	0.7(0.5)	1.5(1.2)	2.99	0.22
4 <sup>th</sup> week	1.4(1.3)	0.8(1.0)	1.6(1.5)	2.22	0.33

**Table 4:** State of readiness of chronic leg ulcers for skin grafting after 4 weeks of treatment.

State of ulcer	clinical Score	honey	mixture	phenytoin
Healed	0	0%	0%	22%
Would heal (needed no graft)	1	12%	11%	11%
Absolutely ready for graft	2	23%	22%	11%
Relatively ready for graft	3-4	59%	56%	28%
Net ready	5-9	6%	11%	28%

## Discussion

Phenytoin and honey have been demonstrated in previous studies to enhance wound healing when compared with conventional treatment [3-10]. It was therefore not necessary to include a conventional treatment group in this study. Honey consists of 80% carbohydrate in form of fructose and glucose. The remaining 20% is mainly water. There are also vitamins and trace elements along with an enzyme system called "inhibine". These are peroxidases that release oxidants (oxygen radicals) which are toxic to microorganisms. When applied topically, substrates like monosaccharides, trace elements and vitamins are made available locally for enhancement of epithelialisation, and granulation tissue formation. In addition, its rather low PH, high osmolality and enzyme confer on it an antiseptic property.

As can be seen in the percent reduction in size of the ulcers from commencement to the end and at the end week of the experiment our study suggests that phenytoin may be superior to honey in treatment of chronic ulcers. The rate of healing and the number of ulcers that progressed to healing with phenytoin during the four weeks of study was less than those reported in studies on abscess cavities [6], and on chronic skin ulcers. This variation of result may be explained partly by the fact that our cases were outpatients and therefore ambulant, and partly by the long duration of their ulcers. The ulcers were also rather large.

Based on the clinical score, best initial response was seen in the honey group. Clinical response with phenytoin

however was not noticeable until later on in the 3<sup>rd</sup> and 4<sup>th</sup> weeks of treatment. This study is the first of its kind to compare phenytoin and honey in wound healing. A previous study [8] had demonstrated the enhancement by phenytoin and its superiority over polyurethane membrane drape and topical soframycin on lower limb partial thickness skin donor sites. Phenytoin appears to have a greater tendency to accelerate healing of acute wound than those that are chronic. The difference in effect may be explained by the indirect action of phenytoin on healing. Lodha *et al.* [6] in their clinical and laboratory experiments had suggested that phenytoin acts by decreasing local oedema through anti-inflammatory action of stabilizing cell membrane and reducing calcium dependent release of various cellular products including lysozymes and collagenase. Since the inflammatory component of chronic ulcer is minimal, there is little surprise that phenytoin effect is less noticeable in them than in acute wounds. The lack of direct effect on human epidermal keratinocytes and skin fibroblasts has been confirmed in an *in vitro* study [11].

Many patients on topical honey treatment experience some peppery sensation on the wound. This was not observed in the cases treated with phenytoin. Also at the end of four weeks of treatment, the best pain relief was noticeable in the phenytoin group. None of the complications of phenytoin was observed in any patient throughout the treatment period. One of the complications of treatment with honey is excess granulation particularly when there is a delay in skin grafting. This excess granulation effect of honey prompted our introduction of a phenytoin/honey mixture group. However, results obtained in this group appeared generally inferior to those in the other groups. We have noticed that deep wounds (like abscess cavities, undermined ulcers, punched out ulcers) when commenced in honey, till granulation fills the cavity, may subsequently be treated with phenytoin. When honey is discontinued and phenytoin treatment started, excessive granulation is avoided and a complimentary effect obtained. This constitutes a useful tool in treatment of chronic ulcers particularly in getting them prepared for skin grafting. Also, a comparison of the two substance in the repair of wounds intended for healing by primary intention is indicated. Biochemical and microbiological studies in this area are warranted.

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