

# Topical phenytoin effect on pressure ulcers healing: A literature review of the evidence

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A pressure ulcer (PU) is a localised injury to the skin and / or underlying tissue usually over a bony prominence, because of pressure, or pressure in combination with shear (EPUAP/ NPUAP/ PPPPIA 2014). Bennett et al. [1] claimed total cost for PUs management in the UK up to £2.1 billion annually, or 4% of the total UK healthcare expenditure. Thomas et al. [2] reported that only 62% of stage 4 ulcers ever heal. Various PUs treatment methods include ultrasound physiotherapy, UV-radiation and laser-therapy, adequate nutritional supplementation, negative pressure dressings and a wide range of dressings and local ointments and creams [3,4,5].

Introduced in 1937, oral phenytoin was used to treat convulsive disorders [6], with gingival hyperplasia (an increase in the size of the mouth gums) as a common side effect [7]. This stimulatory effect on connective tissue has prompted studies to examine its effects on wound healing [8]. Researchers have suggested that topical phenytoin (PHT) stimulates fibroblast proliferation, facilitates collagen deposition, antagonises glucocorticoid, and activates bone marrow mononuclear cells and endothelial progenitor cells [9,10,11]. PHT decreases wounds bacterial load, although the exact mechanism is not known [12]. Previous studies have suggested its role in managing traumatic wounds [13], abscesses [12], leprosy trophic ulcers [14], chronic wounds [6], skin graft donor site [15], venous stasis ulcers [16], diabetic ulcers [17], burns [18] and decubitus ulcers [19].

Cullum and Petherick [20] reviewed the application of PHT in treating PUs and concluded that it was an experimental treatment that is rarely used in clinical practice and the evidence was of low quality. However, their review assessed only one preparation (ointment), and believed it increased healing rate compared to hydrocolloid and standard

dressings. Also, their literature review included work up to 2007 where only two randomised clinical trials (RCTs) were available. Further publications, including double blinded RCTs and case series, have followed. This assignment will review and analyse previous and up to date studies examining the use of different preparations of PHT in PUs management.

## Literature review

A wide spectrum of methods have been used in the treatment of pressure ulcers, such as pressure relief using beds, mattresses or cushions and patient repositioning (NICE 2014 [21], Gillespie 2014 [22], McGinnis 2014, McInnes 2015, Moore 2015), biophysical modalities such as massage therapy, ultrasonic waves, ultraviolet irradiation, stimulatory micro electrical currents and laser treatment [23,24,25,26,27], nutritional supplementation [28,29], medical and surgical debridement of necrotic tissue (Witkowski 1991, Moore 2013b), negative pressure wound therapy [30,31], and topical treatments including hydrocolloid dressings and phenytoin [32,33].

Modaghegh et al. [34] compared four PHT formulations (gel, cream, phenytoin-sodium powder, and phenytoin powder) on wounds in a rat model and concluded that phenytoin powder showed the most favourable results. Injectable phenytoin should not be used as its high pH (12) can cause skin damage [35]. Bhatia and Prakash [8] suggested PHT to be cheap, safe to use and well tolerated by patients; rarely causing transient burning sensation on initial application, which can be avoided using pure phenytoin powder instead of phenytoin-sodium. Also, formation of granulation tissue prevents this side effect. A generalised mild rash was also noted, resolving on stopping the treatment [36]. Hypertrophic granulation was noted in 10-36% of patients [37,6]. Lewis and Rhodes [38] reported a lack of measurable serum absorption of PHT after 12-22 days of

application to PUs. Bhatia and Prakash [8] reported systemic absorption of PHT to be minimal. Only one case report showed any significant levels of serum phenytoin [35]; this involved an extensive PU that required 12.5 grams per day to cover PUs.

El-Zayat [13] reported preliminary experiences with PHT in 20 war-victim patients with PUs comparing PHT to normal saline gauze. The size of the control group was not provided. The preparation and dosage of PHT used were not specified. He reported analgesic effects, reduced exudate formation, decreased bacterial load, increased granulation and faster wound healing in the PHT group. No inferential statistical analysis was conducted. Measurement of the analgesia effect was not specified, which could merely be related to the moist effect of PHT. Moist environment promotes wound healing as suggested by Winter [39]. In the treatment group, patients experienced complete wound healing within one to three weeks, with one patient needing skin grafting. The control group took six to eight weeks to achieve similar healing, with five patients needing skin grafting. The author emphasised that PHT is effective in promoting healing as well as is readily available, safe, inexpensive, and easy to use. However, no evidence supporting these assumptions was provided.

Anstead et al. [35] reported a rapid response to treatment with PHT on a large stage 4 sacral PU resistant to conventional treatment and complicated by undermining and sinus formation.

Rhodes et al. [40] reported the first RCT. They compared PHT (PHT: n=18), collagen dressings (CD: n=16) and triple antibiotic therapy (TAO: n=13) in 47 nursing home patients with stage 2 decubitus ulcers, as defined by the Agency for Health Care Policy and Research [41]. The patients were matched for demographics (all above 60), and ulcer size and stage, were randomly assigned to treatment groups, but there was no mention of co-morbidities. Ulcers

were initially debrided and cleansed with saline and hydrogen peroxide before treatments were applied. PHT (100mg suspension) was applied daily using sterile gauze soaks, CD was left in place for one week, were secondary dressings changes, and TAO was applied once daily. The primary end points assessed were complete wound healing determined by reduction of wound size and time to healing. Clinical assessment of wounds was completed at the beginning of the study and with each dressing change. It was not clear who assessed this healing process, which may have caused outcome assessment bias if the wounds were assessed by treating physicians who were not blinded to the treatment allocation. The patients were allocated to treatment groups based on the treatment preference of the randomly assigned physician prescribing the treatment plan. This method of randomisation may have caused selection bias. Also, the use of a placebo control could have increased the strength of evidence.

Fifteen of the forty-seven patients did not complete the study, with death being the most common reason. None withdrew due to treatment reactions. Although the researchers reported that serum concentrations were undetectable, they did not specify timings of these blood tests, and reported that three patients did not have serum concentrations measured. This was because of refusal by the patient, other health problems, and leaving the facility. The median time (days) to complete healing was shorter in the phenytoin group (PHT:  $35.3 \pm 14.3$ , CD:  $51.8 \pm 19.6$ , TAO  $53.8 \pm 8.5$ ), which was statistically significant ( $P=0.011$  for TAO;  $p=0.020$  for CD). They reported a statistically significant ( $P=0.005$ ) reduction in ulcer size and exudate in PHT group compared to the other two groups. However, they did not include data to support baseline equivalence for wound size. They also reported that healthy granulation tissue in the phenytoin group appeared within two to seven days in all subjects on wound inspection by treating physicians, compared to six to 21 days in the standard treatment groups. This was statistically significant ( $P<0.05$ ), though the assessment method used is subjective. Although these outcomes favor PHT over the other two groups, this can be challenged by the poor randomisation and the lack of control group. Lastly, the authors did not specify whether PHT and CD groups were on oral antibiotics, which can bias the treatments outcomes.

The patients reported minimal pain, assessed subjectively. Pain rating scales provide a quick index of pain intensity to

which a numerical value can be assigned [42]. Also, some patients received analgesics for medical reasons, which could affect their pain tolerance. They recruited a dedicated nurse, which can influence the different treatments, making it less applicable for real clinical settings. The sample represents healthier subjects (nursing home patients) compared to more sick in-patients with acute illnesses; where results may be different. The nutritional status of these patients was not addressed, which is an important element in preventing and managing PUs [43,44], and can strongly affect the outcomes. Although the paper reflects favourable outcomes of PHT in treating PUs, the evidence is not well supported, and moreover, multifactorial treatment plans in place at these patients' nursing homes were not adequately addressed in this study.

Hollisaz et al. [32] performed an RCT on 83 paraplegic war-victims with 91 PUs (stages 1 and 2), where they compared Hydrocolloid Dressing (HD,  $n=28$ ), Phenytoin Cream (PC,  $n=28$ ), and Saline-gauze Dressing (SD,  $n=27$ ). The authors stated staging the ulcers according to Shea classification [45] or National Pressure Ulcer Advisory Panel (1989). Authors should have used one system to avoid bias as there is a difference in describing stage 1 and 2 ulcers in-between these two systems. For example, for stage 1 Shea describes involvement of epidermis and exposure of dermis, while NPUAP described intact skin. For stage 2, Shea describes full thickness dermal loss and subcutaneous fat exposure, while NPUAP describes partial dermal loss. The response to treatment (healing) was assessed by measurement of the surface area. All the patients were managed in long-term care units or in their homes for eight weeks by a team of general practitioners and nurses, and the ulcer status was recorded as "Complete healing", "Partial healing", "Without improvement" and "Worsening". These definitions were poorly operationalised. They considered complete healing as restoration of epidermis and dermis, which is different when measured against the two staging systems they used. Partial healing, without improving and worsening were based only on ulcer size. Assessment of healing is a multifactorial process where many other variables should be included. This includes the three-dimensional size (where depth is important), amount of exudate, growth of granulation tissue, characteristics of ulcer edges and shape, and others [46,47,48]. Use of valid and reliable assessment tool in wound healing can significantly increase the accuracy of healing assessment, such as the PUSH tool [49,50].

The authors [32] conclude that complete healing of PUs, regardless of location and stage, was better in the HD group than the PC ( $P<0.01$ ) and the SD ( $P<0.005$ ) groups. However, the results were slightly different on further analysis. For stage 1 ulcers, they reported a statistically significant faster complete healing with HD compared to SD and PC (SD:  $P<0.01$ , PC:  $P<0.005$ ). For stage 2 ulcers, HD was statistically significant compared to the SD treatment only (SD:  $P<0.005$ , PC:  $P>0.05$ ). Analysis according to ulcer site concluded HD to demonstrate faster healing over the other two, which was statistically significant, for ulcers in the gluteal region ( $P<0.005$ ). For ischial ulcers, HD was statistically significantly better compared to SD ( $P<0.005$ ) but not PC ( $P=0.1$ ). Interestingly, in sacral ulcers, HD treatment was not statistically significantly different to either the SD or PC treatment groups. This different result in sacral ulcers could be due to the pressure effect in that area and the heavier bacterial colonisation and other factors [51]. The sample size was relatively large compared to previous trials (15 in El-Zayat [13], 45 in Rhodes et al. [40]). Treatment response was assessed after eight weeks, with no explanation for the treatment period chosen. The trial was single blinded; practitioners who undertook the assessments were blinded to treatment, but not the patients. Recruiting a control group (treated with saline gauze) was valuable, though this is not a widely-used treatment. The groups were homogenous for age, sex, co-morbidities and location (home or nursing institution). However, there were important between-group differences at baseline for ulcer size (mean size:  $5\text{cm}^2$  with PC, vs.  $7\text{cm}^2$  with HD, vs.  $10\text{cm}^2$  with SD;  $P>0.10$ ).

To measure each ulcer's surface area, the ulcer borders were traced on to a paper overlay. This primary schematic representation was then scanned, redrawn and measured by software, and finally compared to the ulcer after treatment. There is a potential for systematic measurement errors, where reliability and validity may be compromised. Also, such measurement methods tend to be unreliable as they give only two dimensional readings and may cause discrepancies between measurements of the same wound when different practitioners are taking readings [52]. The system used by the authors here is subjected to inaccuracy and inadequate assessment of the healing process, a factor that can significantly contaminate the outcomes of the three groups. Lastly, they examined a different preparation of PHT topical cream compared to previous work by Rhodes et al. [40], where they used

suspension preparation soaked in saline gauze, making results difficult to compare between the two studies.

Subbanna et al. [19] performed a prospective, randomised, double-blind clinical trial to examine the use of PHT solution in managing stage 2 PUs [53] in 28 hospitalised patients with spinal cord injury. This was the only trial examining the solution preparation. The control group (n=14) was treated with saline-soaked gauze dressing, while the treatment group (n=14) received PHT (5mg/ml solution). Both treatments were changed once per day for 15 days. The treatment period selected was not explained. Ulcer healing rate, volume and size were monitored at treatment initiation and compared to one day following treatment period completion. The healing rate was assessed by the Pressure Ulcer Scale for Healing (PUSH) [49]. PUSH is a valid measure of PU healing over time and accurately differentiates a healing from a non-healing ulcer [50] and was validated to be sensitive to changes over time [54]. Two of the 28 patients did not continue the treatment because of early hospital discharge. Both groups were homogenous in demographics (age: 31-52 years), clinical parameters, laboratory blood results and PUs (all sacral PUs present for >70 days). No side effects were reported and phenytoin serum concentrations were undetectable. Albumin was within normal limits for all subjects, though nutritional status was not adequately assessed, which is an essential factor to include [43], and the use of albumin in isolation to assess nutritional status may be invalid [55]. The results were favorable for PHT, but not statistically significant (P=0.261 for

PUSH score, and P=0.132 for reduction of ulcer size). This double blinded RCT used a validated healing assessment method. The sample was small, the treatment duration and follow-up were short and the sample examined young patients compared to patients who commonly develop PUs. This may limit the interpretation of the results into realistic clinical practice. However, such a homogenous young sample with less potential for confounding variables such as co-morbidities and nutritional deficiencies may make the outcomes comparison more accurate and statistical differences more significant. These results indicate a weak evidence to support the use of PHT for treating PUs in this specific sample, which could be different in other samples in common practice.

Sinha and Amarasena [56] reported using PHT in treating two cases of non-healing PUs. A 52-year-old paraplegic patient developed multiple PUs resistant to treatment with conventional treatments and healed completely with PHT powder. A 49-year-old developed stage 4 PUs failed to respond to conventional treatment and was managed with PHT powder and alginate rope and reported complete healing after 14 weeks. These results are encouraging, but still represent a weak evidence being case reports, especially in the second case where they used extra agent; alginate rope. Several areas of concern have been raised in this review. Important factors in managing PUs include nutritional support, pressure relieving mattresses, turning patients in beds, infection management and others. These factors were not clear in these studies presented and are important to compare results.

## Conclusion

In summary, the literature review suggests a weak evidence supporting the positive healing effect of PHT on PUs. It was suggested to be inexpensive, safe, easy to use and readily available. The RCTs reporting no adverse effects could be underpowered to detect these adverse effects; especially those with high dropout numbers, where bigger samples could have showed statistically significant effects should they exist. Variable treatment outcomes noted may be attributed to different doses and forms, different healing assessment tools, and various patients' variables (age, comorbidities, nutritional status, PU preventive measures and others). The cost-effectiveness is an important aspect to consider.

With these results, it is reasonable to encourage more rigorous research to consolidate these findings in larger and more diverse samples and different stages of PUs. Larger RCTs with diverse samples and reasonably controlled variables are essential to confirm the clinical significance of PHT for managing PUs and decide optimal dosing, preparation and duration of treatment. This can be addressed by using multicentre study designs. Gaps in the literature and evidence base should be identified and addressed accordingly.

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