Author’s response to reviews

Title: A randomized clinical trial comparing hydrocolloid, phenytoin and simple dressings in the treatment of pressure ulcers

Authors:

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Author’s response to reviews: see over
Dear Sir:
The manuscript entitled “A randomized clinical trial comparing hydrocolloid, phenytoin and simple dressing in the treatment of pressure ulcers” was revised according to the changes and corrections requested by dear reviewer. Moreover, point-by-point responses to the reviewer’s remarks were provided below each comment to address where and how the paper has been revised. Then the revised manuscript was formatted according to the formatting checklist of BMC Dermatology.

With the best wishes
Hossein khedmat

Reviewer's report
Reviewer's report:

General

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

Review of manuscript entitled
“A randomized clinical trial comparing hydrocolloid, phenytoin and simple dressing in the treatment of pressure ulcers.”

I have written a review based on criteria from the Guidance for Industry published by the US Food and Drug Administration.

Reference: Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment
http://www.fda.gov/cder/guidance/3226dft.htm

In my review, I have avoided criteria that are applicable only to pharmaceutical companies that seek regulatory registration of their wound care products. Instead, I employed criteria that a prudent reader of BMC Dermatology would find applicable to any trial of pressure ulcers.

Criterion 1

“The claim (also referred to as the indication) refers not only to the beneficial effects of a product, as determined through clinical investigations, but also to the type of wound for which a product is intended (e.g., venous stasis ulcer, diabetic foot ulcer, pressure ulcer, burn sites, donor sites).

Wounds differ pathophysiologically, making it difficult - if not impossible - to generalize results obtained from a trial conducted in patients with one type of wound to those with another wound type.”

http://www.fda.gov/cder/guidance/3226dft.htm

Reviewer’s response to criterion 1: (Minor Compulsory Revisions)

On page 10, last sentence the authors state, “With the HD efficacy observed in the treatment of pressure ulcer in this study, it might be possible to generalize its effectiveness to other types of surface wounds.” Please delete this sentence. In the statement of limitations in paragraph 3 (page 10), please state the results of this trial do not generalize to stage III or stage IV pressure ulcers and do not generalize to other types of wounds.

Authors response: The text was revised accordingly.

Criterion 2

“A claim of complete wound closure for chronic, non-healing wounds is considered the most clinically meaningful of the claims related to improved wound healing. Complete closure is defined as skin closure without drainage or dressing requirements. Generally, studies to support such a claim would be designed to measure incidence of
complete wound closure in the treatment vs. the control groups by a specified time (landmark analysis). Efficacy success would be defined as a statistically significantly greater proportion of patients assigned active product achieving closure compared to the proportion in the control arm. The prespecified time for endpoint measurement should be based on the natural history of the disease process and the expected response to standard care.”

http://www.fda.gov/cder/guidance/3226dft.htm

Reviewer’s response to criterion 2: I believe the authors fulfilled the criterion 2 above. No revision required.

Criterion 3
“The clinical benefit of wound closure that lasts for a very brief time is, at best, highly limited. In general, trials should be designed such that subjects remain on study and continue to be evaluated at least 3 months following complete closure. The purpose for this follow-up period is to measure durability of the effect and to ensure that the product does not adversely affect durability of closure relative to standard care. For some products, durability of closure is also important for distinguishing wound healing from transient wound coverage.”

http://www.fda.gov/cder/guidance/3226dft.htm

Reviewer’s response to criterion 3: (Minor Compulsory Revisions)
The authors do not report long-term follow-up. If long-term follow-up data are available, then please provide data in the Results section of the manuscript. If long-term follow-up data are not available, then describe the absence as a limitation in the paragraph of limitations on page 10, Discussion section.

Authors response: All completely healed ulcer patients were followed-up by monthly visit of general practitioners for four additional months and at the end, they were also examined by the assessor author. No relapse of ulcer was observed in all trial groups during this period of time (Result section).

Criterion 4
“Measurement of partial healing, if prospectively defined, may demonstrate relevant biological activity and be supportive of the determination of efficacy, but cannot be used as primary evidence of clinical efficacy. Partial healing, per se, is not considered an acceptable wound healing claim because the clinical benefit of statistically significant differences in wound size has not been established.”

http://www.fda.gov/cder/guidance/3226dft.htm

Reviewer’s response to criterion 4: (Major compulsory revisions)
The authors assessed “complete resolution,” “partial resolution,” “without improvement,” or “worsening.” (page 6, line 3) The authors report the outcomes from these assessments in Table 3. In paragraph 1, page 6, there is no definition for “complete resolution.” In paragraph 2, page 6, there is a definition for “complete ulcer healing.” If “complete resolution” is identical to “complete ulcer healing,” then please pick one terminology and use the same terminology throughout the manuscript so the reader will not need to guess the definition. I looked for definitions of “partial resolution,” “without improvement,” or “worsening.” I sought definitions that were quantitative or qualitative, unambiguous, reproducible, and mutually exclusive. I did not find these definitions. Therefore, I am led to assume that these were categorical variables that were scored as subjective, global, assessments by the blinded authors. Please state the definitions in paragraph 1, page 6. When the authors state their definitions, please state “partial resolution compared to ….” The comparison might be to baseline ulcer assessment or baseline ulcer tracing. Likewise, the definition for “without improvement” or “worsening” should state a comparison to some baseline.

On page 11, the second paragraph describes the author contributions. If one blinded
author/investigator scored all ulcers for complete resolution, partial resolution, without improvement, or worsening, then please state this in paragraph 1, page 6. If more than one blinded author scored ulcers for complete resolution, partial resolution, without improvement, or worsening, then please state this in paragraph 1, page 6. If more than one author/investigator scored the categorical outcome, then it is customary to report the kappa statistic for inter-rater concordance. If kappa statistics are not available or low, then please mention this as a limitation in the paragraph of limitations on page 10, Discussion section. If one author/investigator scored all ulcers at the eight-week visit, then kappa statistics are not meaningful and are not required.

**Authors response:** Terminology of the text was revised and one terminology was used throughout the manuscript. Definitions of "partial healing", "without improvement" and "worsening" were mentioned in the Methods section. One blinded author scored all ulcers for complete healing, partial healing, without improvement or worsening and the text was revised accordingly.

**Criterion 5**

"The presence of necrotic tissue, sinus tracts, exudation or transudation, and infection of soft and hard tissues can interfere with ulcer healing. Appropriate debridement procedures for the indicated ulcer should be specifically defined in the protocol. To avoid bias and confounding of treatment effect, ulcer debridement should precede evaluation of ulcer extent and infection. Enzymatic debriding agents, like other concomitant topical products, can confound results in wound product trials and generally should be avoided…The need for additional debridement, performed after study treatment has started, may indicate product-induced wound deterioration. As such it should be documented on CRFs [case report forms] and included in analysis of product safety and efficacy. Discontinuation might be indicated in early trials where little is known about product safety…"

http://www.fda.gov/cder/guidance/3226dft.htm

Reviewer’s response to criterion 5: (Major compulsory revision)

On page 5 (paragraph 3), the authors mention debridement. The text suggests debridement was allowed after study treatment started. Please clarify when debridement was allowed or prohibited during the trial. If debridement occurred during randomized study treatment, then please state this as a limitation in the paragraph of limitations on page 10.

**Authors response:** In case of existence of necrotic tissue, it was debrided before treatment. All debridments preceded ulcer tracing and assignment of the participants to trial groups. No debridment was allowed after treatment was started (Methods section).

**Criterion 6**

"Relief of pressure is critical to outcome for chronic ulcers. Pressure is the principal cause of decubitus ulcers and off-loading is often difficult to standardize because equipment (e.g., type of bed) may not be available at all sites, and compliance with study procedures is labor intensive (e.g., turning). If these critical aspects of effective therapeutic intervention cannot be standardized across all sites, it is important to specify the actual care delivered in CRFs …[case report forms]…and to consider concomitant care in the efficacy analysis… Every attempt should be made to define a regimen that can be uniformly applied across sites and deviations should be captured in the CRFs. http://www.fda.gov/cder/guidance/3226dft.htm

Reviewer’s response to criterion 6: (minor compulsory revision)
On page 5 (paragraph 2), the authors state the general practitioners visited every two weeks to assure comparable adherence. If there were differences between patients in family homes versus nursing homes with respect to concomitant care, then state this as a limitation in the paragraph of limitations on page 10.

Authors response: There were no differences in facilities available for patients in family homes versus nursing homes and all the patients had free access to these victims’ long term care centers (Methods section).

Criterion 7

“If an ulcer becomes infected during a study for a topical wound product, and the investigator prescribes topical anti-microbial treatment, it is recommended that the patient be discontinued from study treatment. Use of concomitant topical medication is discouraged in trials for topical products to avoid confounding of safety and efficacy outcomes… Systemic antimicrobial therapy for target wound infection may become necessary during the treatment period of the study. Whether or not study treatment should be discontinued in this situation should be discussed prospectively and the plan included in the protocol. For example, discontinuation might be indicated in early trials, where little is known about product safety and where infection may signal test product-induced deterioration of the wound…” http://www.fda.gov/cder/guidance/3226dft.htm

Reviewer’s response to criterion 7: (minor compulsory revision)

I ask the authors to state which concomitant therapies were allowed or disallowed during study treatment. If there were differences between patients with respect to concomitant care, then state this as a limitation in the paragraph of limitations on page 10.

Authors response: No concomitant topical or systemic antibiotic, glucocorticoid or immunosuppressive agent was allowed during the treatment period of the study and there was no difference between patients with respect to concomitant care (Methods section).

In addition to the criteria-based comments above, I have the following requests for revisions.

Comment 8: Major Compulsory Revisions

Throughout the manuscript, the authors state the study treated 83 patients with 91 ulcers. The authors’ analyses assume the ulcer is the unit of analysis. If a patient has more than one ulcer, then the authors assume the intra-patient variance is the same as the inter-patient variance. Without more data from the authors, I cannot believe these are valid assumptions. Consequently, I do not believe the 95% confidence intervals reported by the authors are accurate. If the intra-patient variance is not the same as the inter-patient variance, then the 95% confidence intervals need to be adjusted to account for the increased variance. If the authors are not familiar with variance inflation factors, then I suggest a reference on clustered data. (reference: Wears RL. Advanced statistics: statistical methods for analyzing cluster and cluster-randomized data. Acad Emerg Med 2002; 9:330-341.) From a statistical perspective, the outcomes from multiple ulcers within one patient may be clustered. The analysis of clustered data requires special statistical techniques. (reference: Wears RL. Advanced statistics: statistical methods for analyzing cluster and cluster-randomized data. Acad Emerg Med 2002; 9:330-341.)

I do not want the authors to think that I advocate a clustered data analysis for their trial. Instead, I ask them to show the data as if the patient were the unit of analysis. The authors will need to select one ulcer per patient for analysis. I recommend a blinded, random process for selection of the ulcer for analysis. Describe the method for
selecting one ulcer per patient under exploratory analyses in the statistical methods section of the manuscript. If a patient has one ulcer that healed within 8 weeks and another ulcer that did not heal within 8 weeks, then the authors will be susceptible to selection bias if they fail to use a blinded, random process to select the ulcer for analysis. The analysis “one ulcer per patient” was not the primary analysis. I advise the authors to show the data from the “one ulcer per patient” analysis as an exploratory analysis in the penultimate paragraph in the Results section. In paragraph 3, page 6, the authors state, “To keep the strength and dependability of the study, we performed a second analysis considering only one ulcer per patient. The findings had no significant difference with the original analysis.” The authors seem to think their statement will satisfy readers that there was no difference between the analyses done “per patient” or “per ulcer.” I disagree for the following reason. If the authors report the data from a “per patient” analysis, then their paper has a chance to be cited in a future meta-analysis of pressure ulcer trials. When the data are reported “per ulcer,” then the data are not usable in a future meta-analysis.

I contacted the US Food and Drug Administration via the personnel listed in the reference: Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment http://www.fda.gov/cder/guidance/3226dft.htm I requested a consultation from a biostatistician at the US Food and Drug Administration regarding the analysis of one ulcer per patient. For the purpose of analyzing treatment efficacy, the FDA statistician agreed that the appropriate analysis is one ulcer per patient. When analyzing adverse events, then it is appropriate to analyze all ulcers that were treated. Since the authors reported no adverse events, I can find no statistical rationale for an analysis “per ulcer.” If the authors insist on reporting their analysis “per ulcer,” that is OK with me. However, I insist the authors must also report the analysis “one ulcer per patient.”

Authors response: The data regarding “per patient” analysis considering only one ulcer per patient was reported in the penultimate paragraph in the Results section and relevant details were mentioned in table 4. Random number table was used for selecting one ulcer per patient.

Comment 9: Discretionary revision
Page 2, background, line 5
Please change the word “older” to “other.” I object to the word “older” because the reader might equate “older” with “established” or “standard.” Phenytoin cream is neither “established” nor “standard” according to published clinical trials.

Authors response: The text was revised.

Comment 10: Minor compulsory revision
Page 2, methods, line 5
Please change the word “identical” to “comparable.”

Authors response: The text was revised.

Comment 11: Minor compulsory revision
Page 2, methods “worsering”
Please check spelling.

Authors response: The spelling was corrected.

Comment 12: Minor compulsory revision
Please check “deducted” versus “deduced.”

**Authors response:** The spelling was corrected.

Comment 13: Minor compulsory revision
Page 3, background, line 11
Please check “would” versus “wound.”

**Authors response:** The spelling was corrected.

Comment 14: Discretionary revision
Page 4, Methods, first sentence I do not understand the use of the word “nonprobability.” Please explain or delete the word “nonprobability.”

**Authors response:** The word “nonprobability” was deleted.

Comment 15: Revision decision per editor
Page 4, Methods
The authors do not mention an institutional review board. I defer to the editors of BMC Dermatology with regard to the requirement for review by an institutional review board.

**Authors response:** The study proposal was reviewed, approved and granted by Jaonbazan Medical and Engineering Research Center (JMERC) (Methods section).

Comment 16: Discretionary revision
Page 5, line 2 and line 3
The following text “(in these classifications, stage 1 and II are the same, although there is a 15-year interval between them)” is confusing. I recommend deleting the parenthetical statement since the text is clearer without the parenthetical statement.

**Authors response:** The parenthetical statement was deleted.

Comment 17: Minor compulsory revision
Page 5, paragraph 2
The authors state “restricted blocked randomization.”

Page 6, paragraph 2
The authors state “blocked randomization was done.”

I fear the authors used the word “blocked” when they meant to say, “stratified.” Please check and correct.

**Authors response:** The word “restricted” was deleted.

Comment 18: Minor compulsory revision
Page 5, paragraph 3, line 2
I do not understand the use of “normal saline serum.” I assume the authors meant “normal saline.”

**Authors response:** The text was revised accordingly.
Comment 19: Discretionary revision
Page 6, line 5 “exploiting a software...” Please state the name of the software.

Authors response: AutoCAD 2000 software was used for ulcer tracing and measurement.

Comment 20: Minor compulsory revision
Page 6, line 7 “softwore” Please check spelling.

Authors response: The spelling was corrected.

Comment 21: Minor compulsory revision
Page 7, line 9 “precluds” Please check spelling.

Authors response: The spelling was corrected.

Comment 22: Minor compulsory revision
Page 7, line 12
The authors imply they were blind to treatment assignment when they assessed the 8-week outcome. I ask the authors to describe in one or two sentences how they maintained their blinded status. The rationale for my request may be found in the CONSORT.

Authors response: To maintain blinded status on assessment of outcomes, after ulcer dressing had been removed by the general practitioner, the assessors should examine the patients without asking anything about their trial group. The gross appearance of the ulcers without dressing, whether they were healed or not, were indistinguishable in terms of administered intervention. The assessor was also asked to try to identify which treatment had been administered to each patient at the time of 8-wk outcome assessment. On the whole, 27.7% of his guesses was correct (25% in HD group, 32.1% in PC group and 25.9% in SD group). Thus, the assessor ability to accurately guess their group assignment was not better than chance, i.e. there was no significant difference among three trial groups with respect to proportions guessed correctly (P>0.2 in all cases).

Comment 23: Minor compulsory revision Page 7, line 23 “testes” Please check spelling.

Authors response: The spelling was corrected.

Comment 24: Discretionary Revision
Page 8, line 5 through line 22
The authors use the term “effect size” in multiple sentences in the manuscript. Some readers may misunderstand the term “effect size” since there are many types of effect size. For example, the effect size can be defined as the difference between two means divided by the pooled standard deviation. The authors will be less likely to mislead
their readers if they use standard nomenclature published in the glossary of the ACP Journal Club. I believe in every usage of “effect size” on page 8, the authors were reporting “absolute risk reduction” as defined by the ACP Journal Club.

(Glossary. ACP J Club. 2004 Jan-Feb; 140(1):A19)

**Authors response:** The term "effect size" was defined in Methods section.

Comment 25: Major compulsory revision

Page 8

I attempted to calculate absolute risk reductions and 95% confidence intervals using the data in the text. The method I used came from page 29, Fleiss: Statistical Methods for Rates and Proportions, Wiley, 1981. The 95% confidence intervals I calculated were wider than the intervals reported in the manuscript. The discrepancy does not bother me if the authors used a different method for calculating confidence intervals. For the primary analyses, I require the authors to report the name of the statistical software or the reference for the technique used to calculate the 95% confidence intervals.

**Authors response:** 95% confidence intervals were calculated by the formula:

\[
95\% \text{ CI} = \text{Effect size} \pm Z_{1 - \frac{\alpha}{2}} \sqrt{\frac{p_1 (1 - p_1)}{n_1} + \frac{p_2 (1 - p_2)}{n_2}}
\]

\(\alpha = 0.05\)

\(P_1 = \) Response rate to new therapy (HD)

\(P_2 = \) Response rate to other therapies (SD or PC)

\(n_1 = \) Number of subjects received new therapy (HD)

\(n_2 = \) Number of subjects received other therapies (SD or PC)

Our reference:


Comment 26: Minor compulsory revision

Page 8

In the subgroup analyses, some of the cells have fewer than 5 observations. The authors will need to show they used the appropriate statistical technique for rare events. Another alternative for the subgroup analyses is to display the raw data without 95% confidence intervals and without tests of inference or estimation.

**Authors response:** For rare events (more than 20 percent of cross tabulation cells with values less than 5), Fisher's exact test was used.

Comment 27: Discretionary revision

Page 8, discussion, first sentence

Please check grammar.

**Authors response:** The text was revised.

Comment 28: Discretionary Revisions

Page 9, line 1
The authors use the word “locally.” Do they mean, “locally” as in Tehran, or do they mean, “locally” as in “topically.”

**Authors response:** The text was revised.

Comment 29: Discretionary Revisions
Page 9, paragraph 2
“Different benefits of this method in comparison with…more convenience and less pain.”
Please insert here the references for these assertions.

**Authors response:** New references were inserted.

Comment 30: Minor compulsory revisions
Page 9, paragraph 3
“Hydrocolloid dressings or adhesives absorb…”
Please check grammar. “that is vulnerable and is retrieving” Please reconsider choice of words. “activating granloctyes” Please check spelling.
“monocytes and complement system.”
Please insert here the references for these assertions. “and will ensue ulcer’s autodebridement.”
Please insert here the references for these assertions. “much lower than the other usual treatment methods.”
Please insert here the references for these assertions.

**Authors response:** The text was revised accordingly.

Comment 31: Discretionary Revisions
Page 10, lines 1 and 2
Please insert here the references for these assertions.

**Authors response:** The references were inserted.

Comment 32: Minor compulsory revisions
Page 10, paragraph 3
“The lower healing effect of HD on sacral ulcers…pressure effects in this area or more bacterial colonization.”
Please insert here the references for these assertions.
Please add the small number of gluteal and sacral ulcers preclude definitive statements about differences between treatment subgroups.

**Authors response:** The references were inserted and the recommended statement was added.

Comment 33: Minor compulsory revisions
Pages 11-14
There are several typographical errors in the reference list.

**Authors response:** The reference section was extensively edited.

Comment 34: Major compulsory revision
Table 2:
The title for table 2 is “Comparison of pressure ulcer variables in 3 treatment groups…”
I do not believe the title is correct. If the title were correct, then I would read the table and assume the mean age of ulcers was 36.63 y and the mean weight of ulcers was 61.12 kg. I believe the authors will prefer that I read the table as the mean age of patients was 36.63 y, and the mean weight of patients was 61.12 kg. Therefore, the correct title for the table 2 is “Baseline characteristics for patients assigned to hydrocolloid, phenytoin, or simple dressing.” The column on the far left must contain the number of patients (total n = 83). All the cells in table 2 need to be corrected to reflect one ulcer per patient. In the methods section, define a process without selection bias to select one ulcer per patient.

Authors response: The title and the cells of the table 2 were revised and table 4 was added to reflect data with respect to one ulcer per patient analysis.

Comment 35: Major compulsory revision
Figure 1: Flow diagram of participants through each stage of the study
Please change every box below the top box. Instead of the number of ulcers, state the number of patients. In the figure caption, define the acronym “SCI.”
Authors response: Flow diagram of participants was revised accordingly.

Comment 36: Minor compulsory revision
Figure 2: Patients’ distribution according to treatment group and ulcer location
Although the title says “patients,” the numbers in the figure are numbers of ulcers. I offer the choice to the authors: either change the numbers in the figure to the number of patients or change the title to “Ulcer distribution according to treatment group and location.”
Authors response: The title was revised.

Comment 37: Minor compulsory revision
Figure 3: Patients’ distribution according to treatment group and ulcer stage
Although the title says “patients,” the numbers in the figure are numbers of ulcers. I recommend the authors change the title to “Ulcer distribution according to treatment group and stage.”
Authors response: The title was revised.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:
I have no competing interests. B